



UEPB

**UNIVERSIDADE ESTADUAL DA PARAÍBA
CAMPUS I**

**CENTRO DE CIÊNCIAS E TECNOLOGIA
DEPARTAMENTO DE QUÍMICA
PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA**

EMANUELA COUTINHO LUNA

**ÓLEOS ESSENCIAIS E SEUS COMPONENTES BIOATIVOS PARA USO FRENTE
À DOENÇAS NEGLIGENCIADAS E ARBOVIROSE: UMA REVISÃO**

**CAMPINA GRANDE
2019**

EMANUELA COUTINHO LUNA

**ÓLEOS ESSENCIAIS E SEUS COMPONENTES BIOATIVOS PARA USO FRENTE
À DOENÇAS NEGLIGENCIADAS E ARBOVIROSES: UMA REVISÃO**

Dissertação apresentada ao Programa de Pós-Graduação em Química da Universidade Estadual da Paraíba, como requisito parcial à obtenção do título de Mestre em Química.

Área de concentração: Química Orgânica.

Orientador: Prof. Dr. Francisco Jaime Bezerra Mendonça Junior.

**CAMPINA GRANDE
2019**

É expressamente proibido a comercialização deste documento, tanto na forma impressa como eletrônica. Sua reprodução total ou parcial é permitida exclusivamente para fins acadêmicos e científicos, desde que na reprodução figure a identificação do autor, título, instituição e ano do trabalho.

L961o Luna, Emanuela Coutinho.
Óleos essenciais e seus componentes bioativos para uso frente à doenças negligenciadas e arboviroses [manuscrito] : uma revisão / Emanuela Coutinho Luna. - 2019.
100 p. : il. colorido.
Digitado.
Dissertação (Mestrado em Química - Mestrado) - Universidade Estadual da Paraíba, Centro de Ciências e Tecnologia, 2019.
"Orientação : Prof. Dr. Francisco Jaime Bezerra Mendonça Junior, Departamento de Química - CCT."
1. Óleos essenciais. 2. Leishmaniose. 3. Doença de Chagas. 4. Dengue. 5. Doença do sono. I. Título
21. ed. CDD 615.321

EMANUELA COUTINHO LUNA

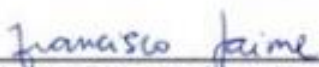
ÓLEOS ESSENCIAIS E SEUS COMPONENTES BIOATIVOS PARA USO FRENTE
À DOENÇAS NEGLIGENCIADAS E ARBOVIROSES: UMA REVISÃO

Dissertação apresentada ao Programa de Pós-Graduação em Química da Universidade Estadual da Paraíba, como requisito parcial à obtenção do título de Mestre em Química.

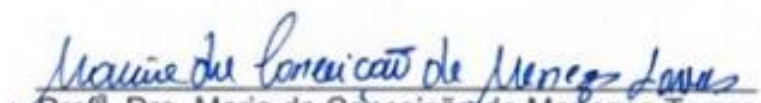
Área de concentração: Química Orgânica.

Aprovada em: 09/12/2019

BANCA EXAMINADORA


Prof. Dr. Francisco Jaime Bezerra Mendonça Junior (Orientador)
Universidade Estadual da Paraíba (UEPB)


Dr. Rodrigo Santos Aquino de Araújo
Universidade Estadual da Paraíba (UEPB)


Prof.^a Dra. Maria da Conceição de Menezes Torres
Universidade Estadual da Paraíba (UEPB)

A minha filha, esposo, pais, irmã e familiares, por todo companheirismo e ajuda, DEDICO.

AGRADECIMENTOS

Primeiramente a Deus, a quem deposito toda minha confiança e fé, por ter me dado forças, saúde, inteligência e coragem, para não desistir diante de tantas limitações.

Ao Professor Francisco Jaime pela orientação, auxílio e atenção durante a realização deste trabalho e de todo o mestrado, por sempre ser disponível a tirar minhas dúvidas e ser um exemplo de profissional.

A minha filha Celina, que em nenhum momento foi empecilho para meus estudos. Mesmo com o cansaço, ela que sempre foi minha motivação à continuar. Obrigada por nessas ultimas semanas dormir direitinho de madrugada, para mamãe conseguir concluir a qualificação. Amo-te!

A meu esposo, Klinger, por tanto amor, zelo, paciência, incentivo, por sempre me ajudar a cuidar tão bem de nossa filha, por ter acreditado em mim e me ajudado a superar minhas limitações e dificuldades.

Aos meus avós, Dorinha e Pedro, pelo amor incondicional, e por todas as orações. Também agradeço a minhas tias, tios e primas, por sempre estarem torcendo por meu bom desempenho e sempre estarem presentes para comemorar minhas conquistas.

Aos meus pais, Luciene e Valter, que sempre acreditaram em meu potencial, e sempre se fizeram presente na minha vida estudantil com muito carinho e apoio, e não mediram esforços para que eu chegasse até esta etapa de minha vida. A minha irmã Gabi, minha amiga, por ser meu referencial de inteligência, perseverança e dedicação aos estudos, por sempre dizer que eu consigo que eu sou capaz.

De modo especial, agradeço a muitas pessoas queridas que se dispuseram a cuidar de Celina. Aos meus pais que abdicaram de suas obrigações para suprirem as minhas necessidades, ficando com Celina todos os dias, para que eu pudesse estudar, e ir as aulas. Ao meu sogro Claudemir, Sogra Vânia, cunhados Bruno e Aline, Cunhas Amim por fazer meu abstract, a Dayzzy e Helena por toda força e palavra de apoio, a Rejane, minhas tias One, Lú, Keka, a Gabi e Thallis, minhas primas irmãs Lê e Sol, que cuidaram muito bem de minha filha em minha ausência.

Aos meus amigos da graduação e pós, em especial Lidiane, Ana Carla, por todos os momentos de estudos, de sorrisos e companheirismo, que nunca serão esquecidos, e levarei essas amizades para o resto da vida.

A Antônio Nóbrega por ser um professor presente desde minha graduação e sempre está disposto a ajudar os alunos.

A PRPGP por todo apoio, em especial Professora Maria José, Sandra, Alexandra, Ernani e Roberto. Agradeço também a Eli Brandão e Márcia, por toda ajuda. Vocês conquistaram a minha admiração

E por fim, a CAPES pelo apoio financeiro durante meu mestrado.

"O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Código de Financiamento 001."

RESUMO

Essa dissertação é uma revisão bibliográfica que versa sobre as doenças negligenciadas (doenças com maior incidência em países subdesenvolvidos, e que acometem sobretudo a parcela da população de mais baixa renda) e o potencial farmacológico que os óleos essenciais têm sobre essas doenças. Das 17 doenças negligenciadas descritas pela Organização Mundial de Saúde, quatro foram selecionadas para esse estudo: dengue, doença de Chagas, leishmanioses e doença do sono. Para compor o banco de dados da literatura, foi realizada uma busca sistemática em vários bancos de dados: PubMed, Web of Science, Medline, Scopus, Science Direct, Scielo, Cochrane Library, plataforma café e Lilacs. A busca foi limitada a artigos publicados nos últimos 10 anos, sem restrição de idiomas, utilizando várias combinações de palavras-chave: “óleos essenciais”, “doenças negligenciadas”, “terpenos”, “fenilpropanóides”, “leishmaniose”, “doença de chagas”, “tripanossomíase americana”, “doença do sono”, “tripanossomíase africana”, “arbovirose” e “dengue”. Essa revisão de literatura deu origem a um artigo que foi publicado na revista *Oxidative Medicine and Cellular Longevity* e que tem como título *Active Essential Oils and their components in use against Neglected Diseases and Arboviruses*. Após a compilação da bibliografia observamos que existe uma vasta gama de óleos essenciais, suas frações ou seus componentes isolados com proeminente atividade sobre as doenças negligenciadas analisadas. Esse estudo poderá ser utilizado como base para selecionar algumas plantas para que se possa dar continuidade aos estudos de suas propriedades farmacológicas, ou para selecionar moléculas mais promissoras, que possam servir como base para a modificação estrutural de novos compostos bioativos com propriedades biológicas mais acentuadas para alguma dessas doenças.

Palavras-Chave: Óleos essenciais. Doenças negligenciadas. Leishmaniose. Doença de Chagas. Dengue. Doença do sono.

ABSTRACT

This dissertation is a bibliographic review that deals with neglected diseases (diseases with higher incidence in underdeveloped countries, affecting mainly the lower income population) and the pharmacological potential that essential oils have on these diseases. Of the 17 neglected diseases described by the World Health Organization, four were selected for this study: dengue, Chagas disease, leishmaniasis and sleeping sickness. To compose the literature database, a systematic search was performed in several databases: PubMed, Web of Science, Medline, Scopus, Science Direct, Scielo, Cochrane Library, Coffee Platform and Lilacs. The search was limited to articles published in the last 10 years without language restriction using various keyword combinations: “essential oils”, “neglected diseases”, “terpenes”, “phenylpropanoids”, “leishmaniasis”, “American trypanosomiasis”, “sleeping sickness”, “African trypanosomiasis”, “arbovirus” and “dengue”. This literature review gave rise to an article that was published in the journal *Oxidative Medicine and Cellular Longevity* and is entitled *Active Essential Oils and their components in use against Neglected Diseases and Arboviruses*. After compiling the bibliography we observe that there is a wide range of essential oils, their fractions or their isolated components with prominent activity on the neglected diseases analyzed. This study could be used as a basis for selecting some plants for further study of their pharmacological properties, or for selecting more promising molecules that can serve as a basis for structural modification of new bioactive compounds with enhanced biological properties to enhance the quality of their research for any of these diseases.

Keywords: Essencial oils. Neglected diseases. Leishmaniasis Chagas disease. Dengue. Sleeping sickness.

LISTA DE ILUSTRAÇÕES

Figura1 – Evolução da salicina até a obtenção do ácido acetilsalicílico.....	17
Figura2 – Estrutura química do paclitaxel.....	18
Figura3 – Exemplos de terpenóides formados a partir da união cabeça-cauda dos isoprenos.....	21
Figura4 – Biossíntese de Fenilpropanóides.....	22
Figura5 – Estrutura química do Timol (IV) e a droga benznidazol (V).....	31
Figura6 – Estrutura química do Geranilgeraniol.....	32
Figura7 – Estrutura química do Linalol.....	32
Figura8 – Estruturas químicas do carvacrol(VI), ascaridol(VII) e óxido de cariofileno(VIII).....	34
Figura9 – Estruturas químicas do isotiocianato de benzila (IX), cinamaldeído (X) oxido de estireno (XI) e (-)- α -cedrene (XII).....	34
Figura10- Estrutura química do Limoneno.....	35
Figura11- Estrutura química do α -bisabolol.....	37
Figura12- Estrutura química do α -terpinene (XIII) e do 3- careno (XIV).....	38

LISTA DE ABREVIATURAS E SIGLAS

DN	Doenças negligenciadas
MS	Ministério da Saúde
NCI	National Cancer Institute
OE	Óleos essenciais
PNPIC	Política Nacional de Práticas Integrativas e Complementares
SUS	Sistema Único de Saúde

LISTA DE GRÁFICOS

- Gráfico 1** - Estudos sobre óleos essenciais no período de 2002 a 2018..... **30**
- Gráfico 2** - Quantidade de plantas com óleos essenciais estudados no período de 2002 a 2018, para a doença de Chagas..... **31**
- Gráfico 3** - Quantidade de plantas com óleos essenciais estudados no período de 2006 a 2018, para a doença do sono..... **33**
- Gráfico 4** - Quantidade de compostos isolados estudados no período de 2006 a 2018, para a Leishmaniose..... **36**
- Gráfico 5** - Quantidade de compostos isolados estudados no período de 2009 a 2015, para a Dengue..... **38**

SUMÁRIO

1	INTRODUÇÃO	12
2	OBJETIVOS	14
2.1	Objetivo Geral	14
2.2	Objetivo específico	14
3	FUNDAMENTAÇÃO TEÓRICA	15
3.1	Plantas medicinais.....	15
3.2	Metabólitos secundários.....	16
3.3	Óleos essenciais	19
3.4	Doenças negligenciadas.....	23
3.4.1	Doença de Chagas	24
3.4.2	Doença do Sono	25
3.4.3	Leishmaniose	26
3.4.4	Dengue	26
4	METODOLOGIA	28
5	RESULTADOS E DISCUSSÕES	29
6	CONCLUSÃO	39
	REFERÊNCIAS	41
	APÊNDICE A – PRODUÇÃO CIENTÍFICA.....	47

1 INTRODUÇÃO

O conhecimento sobre as propriedades terapêutica das plantas no tratamento de enfermidades é milenar, basta citarmos: aspirina, morfina, quinina, digitoxina, que são alguns dos fármacos mais antigos, e que foram obtidos a partir de plantas. As formas de utilização dessas plantas são muito variadas, e incluem a simples ingestão de um chá ou uma bebida, a própria mastigação de uma erva, ou a aplicação de folhas em cima de ferimentos para aliviar sintomas (CHIN *et al.*, 2006). Esse conhecimento milenar despertou, e desperta o interesse de vários pesquisadores ao redor do mundo na busca de novas moléculas, princípios ativos naturais, que possam ser utilizados com alguma finalidade terapêutica. (VIEGAS & BOLZANI, 2006).

Produtos naturais são uma vasta classe de compostos químicos cuja origem é oriunda da biodiversidade (plantas, animais, insetos, fungos, microorganismos, etc). Os produtos naturais oriundos do metabolismo secundário das plantas podem ser classificados em 3 classes principais: alcalóides, compostos fenólicos e terpenóides, que se subdividem em numerosas classes que incluem: flavonóides, cumarinas, lignanas, iridóides, fenilpropanóides, glicosídeos, taninos, terpenos, alcalóides, etc.

Uma das frações vegetais importantes para se obter algumas dessas classes de compostos são os óleos essenciais (OE). Óleos essenciais, também chamados de óleos voláteis constituem a fração que remete ao aroma, cheiro, ou odor das plantas, que por sua vez são ricos em compostos aromáticos. Esses OEs são mais comumente encontrados nas angiospermas dicotiledôneas, principalmente na das famílias Asteraceae, Apiaceae, Lamiaceae, Lauraceae, Myrtaceae. A composição dos OEs pode variar de acordo com a sua localização na planta, pelo clima, solo, época do ano, horário da coleta (SIMÕES *et al.*, 2010).

Os principais constituintes dos óleos essenciais são os fenilpropanóides e os terpenóides. Os fenilpropanóides são derivados da via metabólica do ácido chiquímico, e caracterizam-se por possuir em sua estrutura química um anel aromático unido a uma cadeia de três carbonos. E os terpenos são moléculas derivados do isopreno (2-metil-1,3-butadieno), um hemiterpeno composto por 5 átomos de carbono, que através de combinações entre essas sub-unidades originam os monoterpenos (10 átomos de carbonos), os sesquiterpenos (15 carbonos), diterpenos (20 carbonos), triterpenos (30 carbonos), etc.

Como já mencionado anteriormente, muitas sociedades e comunidades através da medicina popular faz o uso de plantas e partes de plantas para o tratamento de diversas doenças e dentre essas doenças iremos destacar as doenças negligenciadas.

Doenças negligenciadas são um conjunto de doenças causada por várias classes de patógenos infecciosos e parasitários, incluindo protozoários, vírus, bactérias e helmintos. Eles afetam mais frequentemente populações de baixa renda, com maior prevalência em países tropicais e subtropicais. De acordo com a Organização Mundial da Saúde, são um conjunto de 17 doenças, incluindo leishmaniose, tripanossomíase africana e americana, hanseníase, tuberculose, leptospirose, oncocercose, e esquistossomose, que afetam mais de um bilhão de pessoas em todo o mundo e são consideradas uma ameaça à saúde pública em 149 países (WHO, 2012; WHO, 2010).

O fato de essas doenças não serem consideradas prioritárias pelas indústrias farmacêuticas resulta em baixo investimento em pesquisa e desenvolvimento de novos medicamentos, fazendo com que as poucas opções de tratamento disponíveis se tornem obsoletas, precárias, desatualizadas e até mesmo em alguns casos inexistente (MNEDONÇA JUNIOR, 2015). Associado a isso também se observa a falta de atenção dada por parte das entidades políticas, sociais e de saúde, por esses motivos são consideradas doenças negligenciadas, ou esquecidas (YAZBEK, 2012; ASSIS e ARAÚJO-JORGE, 2018; NIKOLAY et al., 2015).

Nesse contexto, o objetivo dessa dissertação foi realizar um estudo bibliográfico visando a atualização das informações disponíveis na literatura sobre o uso dos óleos essenciais, suas frações e seus constituintes químicos isolados como alternativas terapêuticas para o tratamento de algumas doenças negligenciadas: doença de Chagas, doença do sono, leishmanioses e arboviroses, em especial a dengue.

A escolha para estudar essas doenças se deu a partir de revisões de literatura, onde se identificou que a dengue, doença de chagas e leishmaniose, são doenças que se destacam no Brasil, por terem grande índice de mortalidade e escasses de tratamento. Já a doença do sono foi escolhida devido ao grande número de mortes que ela causa, e pouco se houve falar da mesma, conseqüentemente, poucos estudos são feitos.

2 OBJETIVOS

2.1 Objetivo geral

Realizar uma revisão bibliográfica baseada em artigos científicos com objetivo de promover uma atualização das informações disponíveis na literatura sobre o potencial dos óleos essenciais, suas frações e seus constituintes químicos isolados capazes de ser utilizados como alternativas terapêuticas para o tratamento de doenças negligenciadas, tais como doença de Chagas, doença do sono, leishmanioses e arboviroses, em especial a dengue.

2.2 Objetivos específicos

- Realizar uma revisão bibliográfica sobre OEs, suas frações e seus constituintes capazes de ser utilizados como alternativas terapêuticas para o tratamento da doença de Chagas.
- Realizar uma revisão bibliográfica sobre OEs, suas frações e seus constituintes capazes de ser utilizados como alternativas terapêuticas para o tratamento da doença do sono.
- Realizar uma revisão bibliográfica sobre OEs, suas frações e seus constituintes capazes de ser utilizados como alternativas terapêuticas para o tratamento das leishmanioses.
- Realizar uma revisão bibliográfica sobre OEs, suas frações e seus constituintes capazes de ser utilizados como alternativas terapêuticas para o tratamento da dengue.

3 FUNDAMENTAÇÃO TEÓRICA

3.1 Plantas medicinais

Desde a antiguidade, as plantas são utilizadas e conhecidas pelos seus poderes curativos. Os primeiros hominídeos já faziam uso de suas essências, e princípios ativos para combater as enfermidades que os acometiam. E assim, as plantas foram ganhando espaço e se tornaram o principal meio terapêutico para tratamento da saúde das pessoas. Porém, os avanços na saúde foram abrindo espaço para novos métodos de tratamento, e uma dessa maneira os medicamentos industrializados foram gradativamente sendo introduzidos no cotidiano da população. Com isso, as plantas medicinais foram perdendo seu protagonismo e gradativamente sendo substituídas por medicamentos de origem sintética (BADKE et al., 2011).

O Brasil é um dos países onde ainda se faz uso das plantas medicinais para cura e alívio de enfermidades. No nosso país, foi instituída pela Portaria do Ministério da Saúde (MS) nº 971, de 03 de maio de 2006 a Política Nacional de Práticas Integrativas e Complementares (PNPIC) que deve ser empregada pelo Sistema Único de Saúde (SUS). Ela tem por objetivo a ampliação da utilização terapêutica aos pacientes do SUS, garantindo o acesso a plantas e a serviços fitoterápicos, assegurando sua eficácia e qualidade (MINISTERIO DA SAÚDE, 2007).

Um ano mais tarde (2007) foi criado o Programa Nacional de Plantas Medicinais e Fitoterápicos, que visa gerar acesso e uso de plantas medicinais e fitoterápicas aos brasileiros, gerando o uso sustentável da biodiversidade.

Várias pesquisas de grande relevância vêm sendo feita nas áreas de fitoquímica e etnofarmacologia, e são importantes para ampliar os conhecimentos do uso popular de plantas e extratos pela comunidade, assim como para comprovar cientificamente a atividade dos componentes naturais de cada espécie vegetal, além de ajudar na busca de princípios ativos que possam ser utilizados contra as mais diversas enfermidades (GONÇALVES et al., 2017). Os principais destaques da utilização dessas plantas como medicamentos, são seus baixos custos, a disponibilidade de matéria prima, os compostos químicos extremamente diversos, e a grande aceitação da população, sobretudo de baixa renda, dentre outros (ALMEIDA; SCHEFFER, 2012).

No início da história dos fármacos, os materiais vegetais eram utilizados da mesma forma que eram encontrados no meio ambiente, depois percebeu-se que deixando-o mais concentrado era possível melhorar sua intensidade e acelerar sua ação. Com o avanço da química as substâncias começaram a ser estudadas, identificadas, isoladas e sintetizadas. Contudo o senso comum sobre a medicina popular não foi desprezada, pois ela ainda é um importante guia para a identificação de espécies vegetais e suas partes potencialmente terapêuticas (AURICCHIO; BACCHI, 2003).

3.2 Metabólitos secundários

O conjunto de transformações das moléculas orgânicas que são catalisadas por enzimas, é chamado de metabolismo, ele ocorre em todas as células vivas, supre o organismo de energia, renova as moléculas e garante o estado organizado (MARZZOCO; TORRES, 2007).

As rotas metabólicas são estabelecidas, objetivando o maior aproveitamento de nutrientes para atender as necessidades das células. Existem dois tipos de metabólitos, os primários e secundários. Os metabólitos primários englobam sintetizar proteínas, lipídeos, açúcares, celulose, lignina dentre outras substâncias importantes para a realização das funções vitais (CHAMPE et al., 2008).

Já os metabólitos secundários, se diferem dos metabólitos primários, pois apresentam-se em baixas concentrações e estão presentes especialmente em plantas, fungos, algas, entre outros seres vivos. Suas estruturas são complexas e diversas e apresentam em geral pequeno peso molecular (BERG E LUBERT, 2008).

Os metabólitos secundários podem ser gerados a partir do metabolismo da glicose, que possui dois intermediários principais: o ácido chiquímico e o acetato. O ácido chiquímico é precursor dos taninos, cumarinas, alcalóides derivados dos aminoácidos aromáticos e fenilpropanóides, e todos têm em comum a presença de um anel aromático. Já o acetato tem como derivados os alcalóides derivados dos aminoácidos alifáticos, esteróides e terpenóides (LEITE, 2008).

Um exemplo importante que reflete a importância dos metabólitos secundários para o tratamento de enfermidades é a história do primeiro medicamento comercial, que foi obtido a partir do extrato do salgueiro. À 6000 anos as civilizações primitivas já utilizavam o salgueiro não exclusivamente como

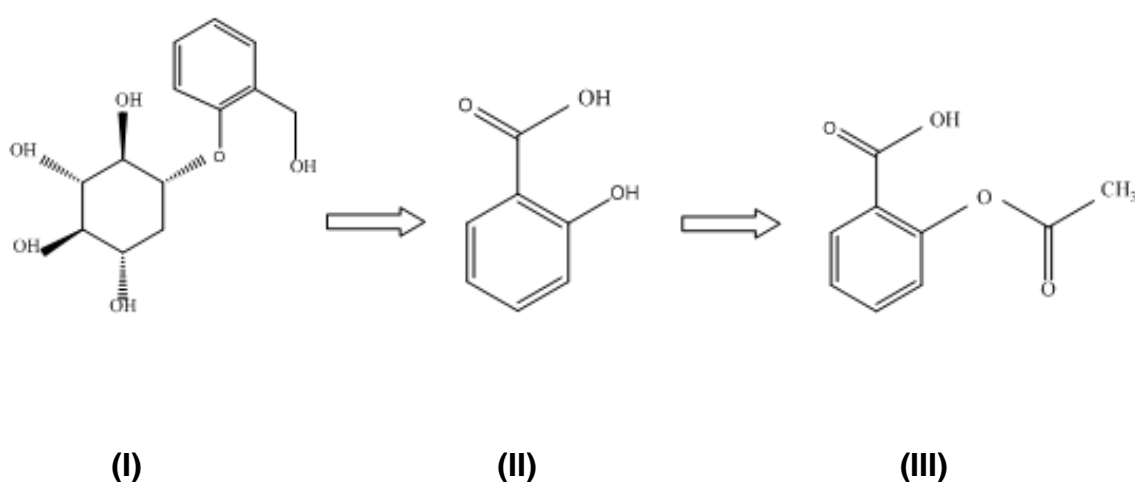
alimento, mas também como alternativa para tratamento de algumas enfermidades, visando diminuir dores, inflamações e febre (LÉVESQUE & LAFONT, 2000).

Os Egípcios (1300 A.C.) usaram as folhas de salgueiro para tratar doenças inflamatórias (NUNN, 1996), no antigo Egito, utilizavam para efeito analgésico e para o alívio das feridas inflamadas (JACK, 1997). Pelos chineses (2000 A.C.) o salgueiro também era utilizado para aliviar febre e dor (RIDDLE, 1999).

A investigação química da substância terapeuticamente ativa do extrato de salgueiro começou no século XIX, onde foi identificado que dentre os componentes ativos do salgueiro estava presente a salicina (um glicosídeo fenólico), porém nela continha muitas impurezas. Em 1828, Buchner, na Universidade de Munique, purificou a salicina, removendo os taninos que havia presente. Ele obteve uma substância amarelada e de sabor amargo. Em 1829, o farmacêutico francês Henri Leroux, obteve a forma cristalina e pura da salicina (I) (LEROUX, 1830; RAINSFORD, 1984).

A salicina era composta por metades de *D*-glicose e álcool salicílico. Esse álcool salicílico foi oxidado originando a ácido salicílico (II), que em 1897 foi acetilado quimicamente por Felix Hoffmann, dando origem ao conhecido ácido acetilsalicílico (III) (RAINSFORD, 1984).

Figura 1: Evolução da salicina até a obtenção do ácido acetilsalicílico.



FONTE: Própria autoria

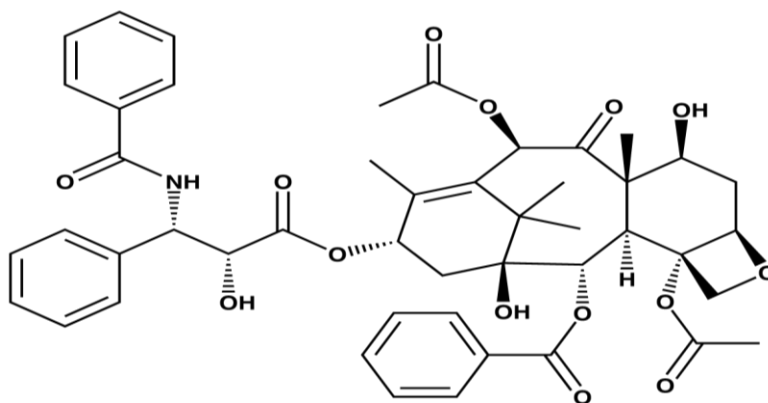
A droga mais antiga a ser sintetizada, o ácido salicílico foi derivada de um metabólito secundário de um vegetal.

Muitas drogas utilizadas atualmente na quimioterapia são também derivados de metabólitos secundários, como por exemplo: os alcalóides de vinca (vinblastina, vincristina, vinorelbina, as lignanas epipodofilotoxinas (etoposídeo, teniposídeo), os diterpenos de taxano (paclitaxel e docetaxel) e os alcalóides derivados da camptotecina (topotecano, irinotecano) (CHABNER e BRUNTON, 2005; DEVITA et al., 2008).

Na década de 50, iniciaram-se as pesquisas para identificar compostos extraídos de plantas que tivessem atividade anti-neoplásicas, com isso foram descobertos inicialmente os alcalóides de vinca. Anos mais tarde, em 1960, o Instituto Nacional do Câncer dos Estados Unidos da América (NCI, do inglês, National Cancer Institute) descobriu os taxanos (CRAGG, 1998).

O paclitaxel (Figura 2), também conhecido como Taxol foi o primeiro representante da classe dos taxanos a ser consentido pela FDA - Food and Drug Administration (Administração Federal de Alimentos e Medicamentos), em 1992 (NOBILI et al., 2009; GLIGOROV e LOTZ, 2004; MA e WANG, 2009).

Figura 2: Estrutura química do paclitaxel



FONTE: adaptada de Pan et al., 2009

Esse nome “Taxol” foi dado, pois tem a presença de um grupo hidroxila, e também naquela época era de costuma colocar o nome do gênero da planta (WALL

E WANI, 1996; WALSH, 1998; GINSBERG, S/D). Sua estrutura química só foi descoberta por volta de 1971, pois ocorreram algumas dificuldades e impediu seu desenvolvimento como antineoplásico em escala industrial. Algumas delas foram: Baixa solubilidade em água, baixo rendimento de extração em *Taxus brevifolia*, e seu crescimento lento (JENNEWEIN e CROTEAU, 2001; SINGLA et al. 2001), assim, o NCI não demonstrou interesse em estudos pré-clínicos do taxol (WALL e WANI, 1996). Após 1975, este voltou a ser interesse do NCI, por sua forte atividade contra a melanona B16 (tumor metastático), sendo capaz também de causar regressão de tumores mamários (KINGSTON, 2005; WALL e WANI, 1996; CRAGG, 1998).

Em 1979 Susan Hortwiz e os seus colaboradores descobriram o mecanismo de ação do taxol. Este fármaco inibe a mitose em células em divisão (KRAITZER et al., 2012; SCHIFF et al., 1979). Devido a sua grande eficácia, a procura por este fármaco tem sido crescente, e hoje é considerado um dos fármacos anticancerígenos mais importantes na clínica para o tratamento do cancro do ovário, da mama e do pulmão, dentre outros (ALTMANN E GERTSH, 2007).

3.3 Óleos essenciais

Os óleos essenciais também conhecidos como óleos voláteis, são derivados de compostos aromáticos, que nos remetem a aroma, cheiro, odor, e de modo especial são encontradas nas plantas (MENEZES, BRITO, LUCCHESI et al., 2017). Através da quimitaxonomia podemos afirmar que os óleos essenciais são encontrados de forma mais abundante nas angiospermas dicotiledôneas, atualmente chamadas de eudicotiledôneas, como as pertencentes às famílias Asteraceae, Myrtaceae, Rutaceae, dentre outras. São encontrados também nas monocotiledôneas, mas, de forma bem limitada às famílias Poaceae e Zingiberaceae (SIMÕES, 2004).

Os OEs são encontrados em uma grande diversidade de plantas odoríferas. São encontrados em forma de líquido hidrofóbico concentrado, e são obtidos em diferentes partes das plantas (ZHU, HENDERSON, et al, 2001).

As diferentes partes das plantas que eles podem ser extraídos são folhas, flores, caules, sementes, raízes ou cascas, brotos, madeiras, e seu armazenamento ocorrem em células secretoras (SIMÕES, 2004). Dependendo de qual parte da

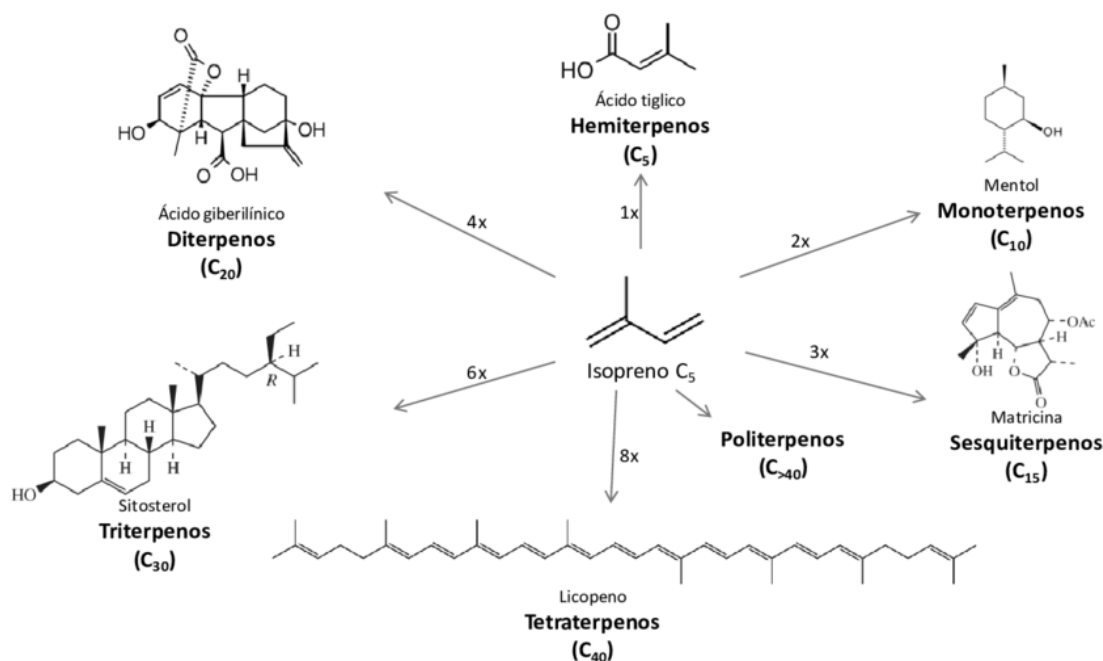
planta for extraído esse óleo essencial, pode variar sua composição química. Vários outros fatores interferem de forma direta na composição desses óleos, mesmo ele sendo extraído do mesmo órgão de uma mesma espécie de planta: temperatura, umidade relativa, características do solo, exposição ao sol, época do ano da colheita (BAKKALI, F; AVERBECK, S.; AVERBECK, D., 2008).

Sua composição química é de grande complexidade, pois estão presentes constituintes muito funcionalizados, porém os constituintes principais pertencem a duas classes químicas: os terpenóides e os fenilpropanóides.

Os terpenóides são quimicamente bem diversificados, tendo sido isolados da natureza aproximadamente 55.000 constituintes diferentes, contendo diferentes esqueletos carbônicos e grupos funcionais oxigenados diversos, tais como os fenóis, ésteres, álcoois, aldeídos, cetonas, éteres, peróxidos.

De acordo com a figura 3, o isopreno (2-metil-1,3-butadieno), também chamado de hemiterpeno, é o terpenóide mais simples (MAFFEI ME, 2010), que contém em sua cadeia carbônica cinco átomos carbonos (C5). Essas unidades de isopreno vão sendo metabolizadas nas plantas, pela ação de vários estímulos genéticos, originando outros terpenóides. Como por exemplo, os monoterpenos, com 10 carbonos em sua cadeia (C10), sesquiterpenos, com 15 carbonos (C15), diterpenos, com 20 carbonos (C20), triterpenos, com 30 carbonos (C30), tetraterpenos, com 40 carbonos (C40), possuindo assim outras classificações de acordo com a quantidade de unidades de isopreno presente na molécula (MENEZES, BRITO, LUCCHESI et al., 2017).

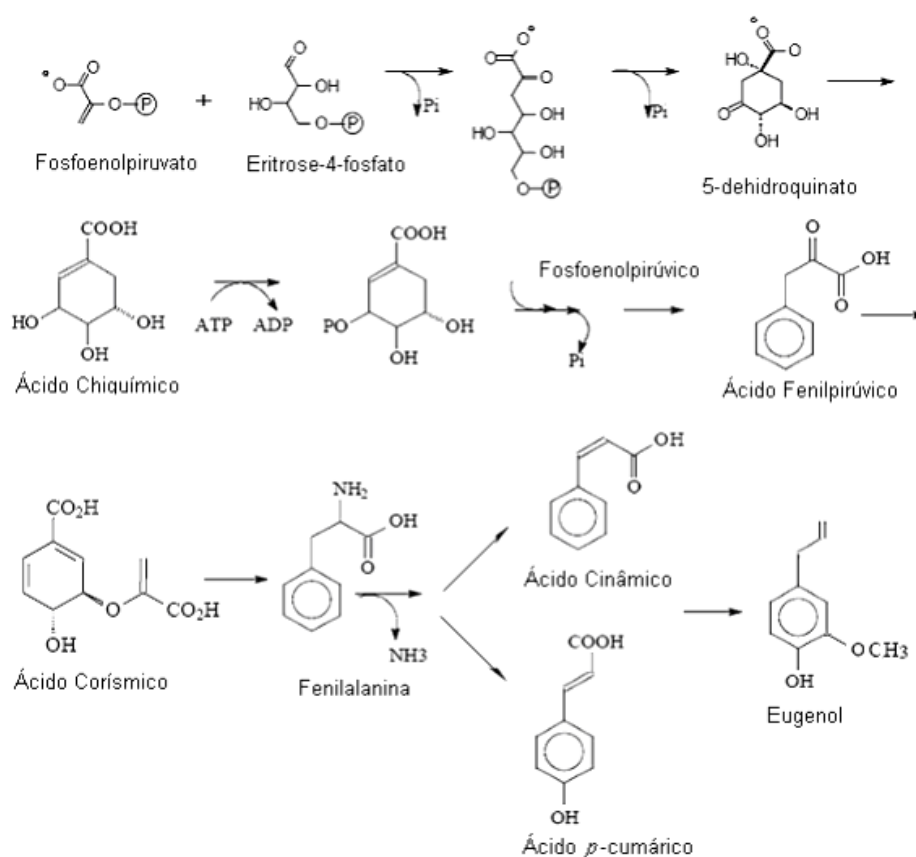
Figura 3: Exemplos de terpenóides formados a partir da união cabeça-cauda dos isoprenos.



FONTES: MENEZES, BRITO, LUCCHESI et al., 2017

Os fenilpropanóides são constituintes comuns de óleos essenciais de plantas, os mais conhecidos são: eugenol, metil eugenol, miristicina, elemicina, chavicol, metil chavicol, dilapiol, anetol, estragol, apiol (SANGWAN et al. 2001). Como podemos observar pela figura 4, eles são substâncias naturais que possuem em sua composição um anel aromático unido a uma cadeia de três carbonos e são derivados do ácido chiquimico e de uma molécula de fosfoenolpiruvato ocorre a formação do ácido corísmico (PERES, 2004). O ácido corísmico gera aminoácidos aromáticos ao qual sofrem ação enzimática e dá origem ao ácido cinâmico ou ao ácido *p*-cumárico (*p*-hidroxicinâmico) (LORENZO et al., 2002).

Figura 4: Biossíntese de Fenilpropanóides



FONTE: LORENZO et al. 2002 e PERES, 2004.

Para obtenção dos óleos essenciais, vários métodos podem ser empregados, incluindo hidrodestilação, microondas, maceração, extração por solventes orgânicos, enfleurage, extração com fluido supercrítico de CO₂, sonicação e prensagem (SANTOS; ALVES; FIGUEIREDO; NETO, 2004).

O uso dos óleos essenciais é bastante difundido, sendo utilizados desde o século XVI. Por volta do século XX eles começaram a ser comercializados nos ramos da perfumaria, cosmética e alimentícia. Porém atualmente, seus principais usos e maior importância comercial se dão na área farmacêutica, onde seus usos ajudam a melhorar curar ou prevenir diversas enfermidades. Suas aplicações incluem usos como repelentes, antiinflamatórios, anticâncer, antimicrobiano, antiasmático, antioxidante (GAUTAM, MANTHA, MITTAL, 2014). Sendo também bastante utilizado para tratamento de parasitoses e doenças negligenciadas.

3.4 Doenças negligenciadas

Na década de 1970, o termo doenças negligenciadas foi utilizado pela primeira vez, e seu objetivo era se referir a doenças transmissíveis, causados por agentes infecciosos e parasitários, predominantemente em países subdesenvolvidos, e que atinge sobretudo população de baixa renda. O governo nunca deu devida importância e o financiamento para desenvolvimento de medicamentos para essas doenças foi sempre escasso, deixando apenas alternativas terapêuticas precárias e/ou inexistentes, daí o nome, negligenciadas (esquecida) (MENDONÇA JUNIOR, 2015).

Essas doenças são consideradas as que acometem mais fortemente populações historicamente vulneráveis, e que atraem recursos escassos de países e empresas, e elas se proliferam mais facilmente em ambientes de habitacionais precárias. E elas persistem devido a alguns fatores, como exemplo a falha na ciência com pouco conhecimento, a falha no mercado com medicamentos e vacinas caras, falha na saúde pública (MOREL, 2006).

Chirac e Torrele (2006) fizeram uma pesquisa sobre a quantidade de entidades químicas existentes durante os anos de 1975 e 2004, e chegaram a um valor de 1.556 novas entidades químicas, e dentre elas, apenas 21 se dedicam a estudar doenças negligenciadas, ou seja, menos de 1%. E essa porcentagem não sofreu alteração nos últimos 10 anos.

As doenças negligenciadas como muitos pensam, não prevalecem só em meio a grande índice de pobreza, mas contribuem de forma efetiva para a desigualdade e desenvolvimento social (MINISTÉRIO DA SAÚDE, 2010). A ANVISA (Agência Nacional de Vigilância Sanitária), afirma que essas doenças afetam o crescimento populacional, desenvolvimento intelectual e produtividade de trabalho (ANVISA, 2007).

Segundo dados da Organização Mundial da Saúde (OMS), mais de um bilhão de pessoas estão infectados com uma ou mais doenças negligenciadas, esses dados representam um sexto da população mundial.

Mesmo existindo recursos para financiar os pesquisadores que se empenharem a estudar temas relacionados às doenças negligenciadas, as indústrias farmacêuticas não demonstram interesse, devido ao pequeno retorno

lucrativo, visto que a população mais atingida é de baixa renda, em sua maioria, nos países em desenvolvimento (MINISTÉRIO DE SAÚDE, 2010).

Em 2007 houve uma agenda global onde se definiu dezessete doenças negligenciadas que são alvo de ações transnacionais: Doença de Chagas, Dengue, Úlcera de Buruli, Cisticercose, Dracunculíase, Equinococose, Fasciolíase, Tripanossomose humana africana, Leishmaniose, Hanseníase, Filariose linfática, Oncocercose, Raiva, Esquistossomose, Helmintíase, Tracoma, Boubá e Chikungunhya (WORLD HEALTH ORGANIZATION, 2007).

O Programa de Pesquisa e Desenvolvimento de Doenças Negligenciadas, definiu sete doenças como sendo prioridade para o Brasil: Dengue, doença de Chagas, Leishmaniose, Hanseníase, malária, esquistossomose e tuberculose (MINISTÉRIO DA SAÚDE, 2008).

Para comprovar a falta de assistência há essas doenças, o Instituto de Pesquisa Econômica Aplicada, publicou em 2011 um texto que fala sobre os gastos do Ministério da Saúde com medicamentos, e os dados obtidos foram: o gasto total por ano é em média 1,8 bilhões, enquanto a parte utilizada para medicamentos de doenças negligenciadas é de apenas 25 milhões por ano. Os medicamentos para essas doenças foram lançados no mercado a pouco mais de 40 anos, e nesse período pouco houve avanço, e os medicamentos disponibilizados pouco supre a demanda (MENDONÇA JUNIOR, 2015)

Por exemplo, a AIDS (que até pouco tempo, era considerada uma doença negligenciada), e os gastos direcionados a essa doença era de quase 580 milhões, que dava para atender a necessidade de 180.000 pacientes. Os dados do Ministério da Saúde em 2007 afirmam que apenas 4,6% das despesas eram direcionados para pacientes com AIDS (MENDONÇA JUNIOR, 2015).

3.4.1 Doença de Chagas

A tripanossomíase americana, também chamada de doença de Chagas, tem como agente etiológico o protozoário o *Tripanossoma cruzi*, que é transmitido aos seres humanos através da picada do triatomídeo conhecido como barbeiro. Segundo a Organização Mundial de Saúde ela afeta 7 milhões de pessoas no mundo, é endêmica em 21 países latino americano e é responsável por aproximadamente 7

mil mortes por ano, deixando ainda cerca de 25 milhões de pessoas em risco de infecção. (LUNA, et al., 2018).

A doença de chagas foi descoberta a mais de 100 anos, e junto dessa descoberta, percebeu-se que sua mortalidade e morbidade são elevadas, devido a alguns fatores, dentre eles podemos citar a ausência de vacinas e tratamentos, e até hoje só existem dois remédios para seu tratamento: benznidazol e o nifurtimox.

Esses remédios possuem desvantagens como, por exemplo, alta toxicidade e seus efeitos colaterais são graves. Com isso, percebeu-se a necessidade de novas alternativas terapêuticas, mais eficazes e menos tóxicas, e os produtos naturais se encaixam perfeitamente nesses aspectos. (LUNA, et al., 2018).

Já existem muitos estudos promissores sobre óleos essenciais com atividade biológica contra essa doença, nas últimas décadas a atividade tripanocida de quase 400 espécies foram analisadas. Holetz pesquisou sobre o OE *Ocimum gratissimum*, Santoro pesquisou sobre o OE *Origanum vulgare* e *Thymus vulgares* que são conhecidos popularmente como orégano e tomilho (HOLETZ, et al, 2002). Santoro pesquisou também sobre o cravo da Índia que mostrou um grande efeito farmacológico (SANTORO, et al, 2007). Menna Barreto estudou sobre o extrato etanólico *Pterodon pubescens* e um dos componentes isolados mais ativos foi o geraniolgeraniol (MENNA BARRETO, et al, 2008).

3.4.2 Doença do sono

A tripanossomiase africana, também conhecida como doença do sono, tem como agente etiológico o protozoário *Trypanossoma brucei*, que apresenta como subespécies: *Trypanossoma brucei gambiense*, *Trypanossoma brucei rhodesiense* e *Trypanossoma brucei brucei*, elas acometem respectivamente a África Ocidental, África Oriental e somente em animais. (LUNA, et al., 2018).

Afeta cerca de 30 mil pessoas por ano, distribuída por 36 países considerados áreas de risco. O elevado índice de mortalidade é devido a baixa possibilidade de tratamento. (LUNA, et al., 2018).

Após a inoculação do parasita ao homem, a doença evolui em dois estágios, a primeira fase é a hemolinfática, onde acontece a replicação celular, e a segunda fase é a meningoencefálica onde invade o sistema nervoso central, deixando o doente com dor de cabeça, febre, inchaço nos gânglios, distúrbio do sono.

O tratamento para a doença é a quimioterapia, e existem 4 medicamentos que são utilizados: Suramina, pentamidina, melarsoprol e eflornitina, os dois primeiros agem no 1º estágio da doença, e os dois últimos agem no 2º estágio. As suas desvantagens são seu alto custo e a sua produção é ausente de sustentabilidade. Com isso, faz-se necessário a descoberta e desenvolvimento de novas alternativas terapêuticas. (LUNA, et al., 2018)

3.4.3 Leishmaniose

Leishmaniose é um conjunto de doenças infecciosas, mas não contagiosas que tem como agente etiológico parasitas do gênero *Leishmania*.

Assim como outras doenças negligenciadas, a leishmaniose se manifesta em regiões de pobreza, especialmente em 98 países de quatro continentes, América, Europa, Ásia e África. Em 2010 existiam aproximadamente 350 milhões de pessoas com risco de infecção, e que tem estimativa de 2 milhões de novos casos por ano (WHO,2018).

A leishmaniose é dividida em dois tipos: a leishmaniose visceral e a leishmaniose tegumentar. A visceral é a forma mais grave, onde são afetados órgãos vitais e 90% dos casos acontecem em 5 países e o Brasil é um deles. Já a tegumentar é a forma mais comum e se subdivide em leishmaniose cutânea, cutânea difusa e mucosa (WHO, 2010).

Poucas são as opções de tratamento para uma doença que atinge um numero tão grande de pessoas, com as drogas que são utilizadas tendo um pouco mais de 60 anos, que são elas as pentamidina, miltefosina, anfotericina B e paromomicina (FÉLIX, SOUZA E LIMA et al., 2016).

Por isso, os estudos com óleos essenciais vêm aumentando, e no período de 2000 a 2018 foram realizados estudos com aproximadamente 142 espécies de plantas e 44 compostos foram isolados e avaliados contra a Leishmaniose. As famílias que mais foram estudadas são Lamiaceae, Piperaceae e Asteraceae. (KATSUNO, BURROWS, DUNCAN et al., 2015).

3.4.4 Dengue

A dengue é conhecida por duas formas de manifestação, a clássica e a hemorrágica, onde ambas têm como principal vetor o mosquito *Aedes aegypti* e tem

como vetor secundário o mosquito *Aedes albopictus* (LAUGHLIN et al., 2012). Ela é uma arbovirose, ou seja, causada por vírus transmitido por artrópodes.

Segundo a Organização Mundial de Saúde a dengue causa o maior índice de morte comparada a qualquer outra doença arboviral (UNIYAL, TIKAR, R. SINGH et al., 2015). Anualmente ela causa aproximadamente 22 mil mortes em todo mundo (WHO, 2013, VANCHEEF et al, 2013), se proliferando em 100 países, e as principais áreas são as tropicais e subtropicais da América, Ásia, Mediterrâneo Oriental (GUSMAN E ISTURIZ, 2010; WHO, 2013, VANCHEEF et al, 2013).

Seus principais sintomas são dores nas articulações, febre, dor atrás dos olhos, náusea, vômito, erupção cutânea (WHO, 2013). E o seu vetor de transmissão é responsável pela transmissão de outras doenças, incluindo o vírus da febre amarela, Nilo ocidental, encefalite japonesa e transmitida por carrapatos (SAMPATH et al, 2009; STEVENS et al., 2009)

O tratamento dessa doença se dá através de paliativos, pois até o momento as vacinas não estão disponíveis, e não possui medicamento específico. Com isso a melhor maneira de fazer controle da dengue, é quebrando seu ciclo de transmissão, ou seja, não deixando que ocorra proliferação do mosquito. Alguns repelentes já são utilizados, como por exemplo os Termefos (DIAS e MORAIS,2014), mas possuem desvantagens pois causam grande impacto ambiental, são utilizados também os Bioinseticidas eficientes, não causam tanto impacto, mais são de alto custo (206). Por isso, ver-se a necessidade de nossos meios de tratamento e prevenção, e os OE são ótimas opções, visando sua baixa toxicidade. (NAVARRO et al., 2014;)

Assim vários estudos vêm sendo feitos, e em um único artigo de revisão foi estudado cerca de 361 óleos essenciais e sua atividade larvicida, e entre estes mais de 60% foram considerados ativos (DIAS e MORAIS et al.,2014; SRITABUTRA, SOONWERA, et al., 2011; ZHU, 2015). Os monoterpenos foram os mais testados, e os hidrocarbonetos monoterpênicos apresentaram melhor atividade.

4 METODOLOGIA

Para compor o banco de dados da literatura, foi realizada uma busca sistemática em: PubMed, Web of Science, Medline, Scielo - Scientific Electronic Library Online, Cochrane Library.

A busca foi limitada a artigos publicados nos últimos 10 anos, sem, no entanto, desconsiderar alguns artigos de revisão de literatura clássica que também foram consideradas relevantes. Assim, em algumas doenças negligenciadas encontram-se um tempo de pesquisa que abrange períodos de 16 anos.

A pesquisa foi realizada usando várias combinações das seguintes palavras-chave escritas em língua portuguesa, inglesa e espanhola: “óleos essenciais”, “leishmaniose”, “doença de chagas”, “tripanossomíase americana”, “doença do sono”, “tripanossomíase africana”, “arbovirose” e “dengue”.

A seleção do manuscrito foi baseada nos seguintes critérios de inclusão: artigos publicados com palavras-chave no título ou resumo.

Nenhuma restrição de idioma foi aplicada.

A pesquisa foi realizada em 2017 e 2018.

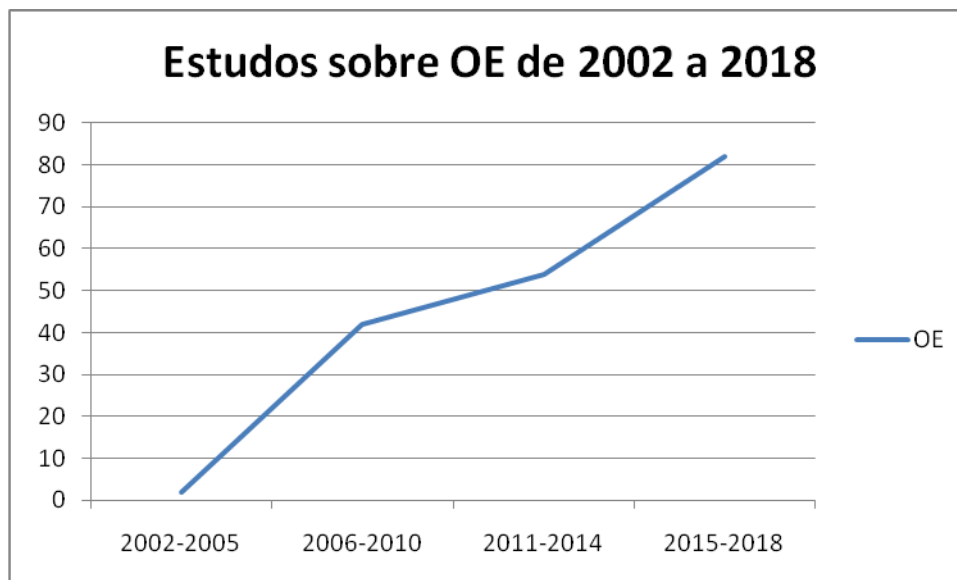
5 RESULTADOS E DISCUSSÕES

Os resultados e discussão aqui apresentados refletem os dados mais relevantes que constam no artigo publicado na revista *Oxidative Medicine e Cellular Longevity*, intitulado “**Active Essential Oils and their Components in Use Against Neglected Diseases and Arboviruses**” (Apêndice A) que foi o principal produto resultado dessa dissertação, onde foi desenvolvida uma revisão bibliográfica a fim de analisar estudos que tinha como objeto, a utilização de óleos essenciais, frações ou componentes isolados que apresentam atividade para doenças negligenciadas selecionadas, dentre elas: Doença de Chagas (Tripanossomíase americana), Doença do sono (Tripanossomíase africana), Leishmaniose e a arbovirose Dengue.

De início, agrupou-se todas as informações no Gráfico 1, e percebe-se o crescimento nos estudos sobre óleos essenciais frente a essas doenças negligenciadas (*T. cruzi*, *T. brucei*, Leishmanioses e Dengue). No período de 2002 a 2005 só foram feitos 2 estudos, de 2006 a 2010 foram estudados 42 óleos essenciais, no período de 2011 a 2014 54 OE foram estudados, e de 2015 a 2018 foram estudados 82 óleos essenciais, até a data de nossa pesquisa para o artigo, mas esses valores no ano de 2018 ainda foram crescentes.

Coincidente, este aumento no número de estudos pode estar relacionado com o crescente índice de mortalidade que acometem a população menos desenvolvida, a grande eficácia e benefícios da utilização de óleos essenciais como forma terapêutica, poucos medicamentos disponíveis, esses e outros fatores contribuem de forma significativa para o aumento na quantidade de pesquisas fazendo com que os pesquisadores aumentem seu interesse pelo tema, que até poucos anos atrás não lhe era dada tanta atenção.

Gráfico 1: Estudos sobre óleos essenciais no período de 2002 a 2018.



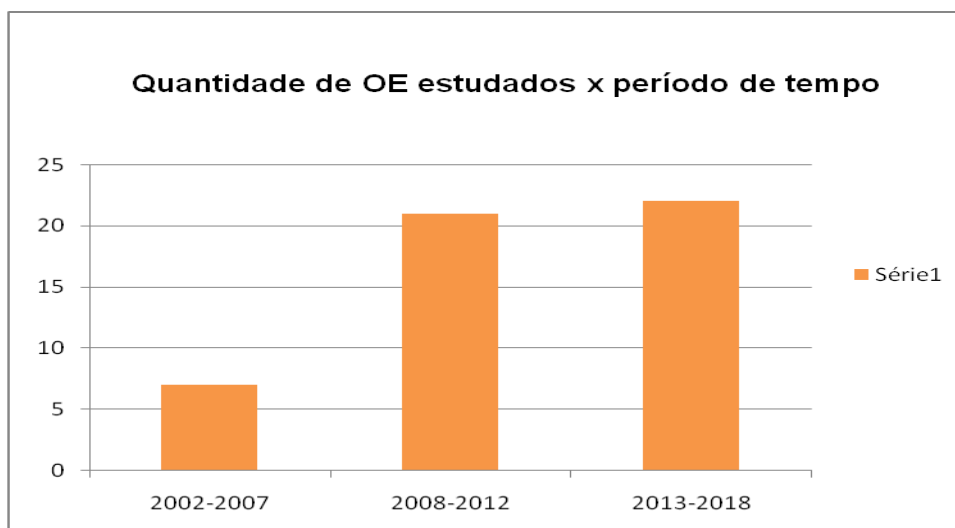
Fonte: Própria autoria

A seguir serão apresentados e discutidos alguns resultados mais relevantes para cada doença negligenciada, que serão apresentados na mesma ordem do artigo, doença por doença, iniciando pela Doença de Chagas. E os resultados na íntegra estão disponíveis no artigo que se encontra no Apêndice.

5.1 Doenças de Chagas

Os artigos que versam sobre *Trypanosoma cruzi* foram obtidos no período de 2002 a 2018, nesses 16 anos foram analisados 50 óleos essenciais de plantas, concentrados em 20 artigos. Percebe-se através do Gráfico 2, que do ano de 2002 a 2007 poucos estudos eram feitos com óleos essenciais com atividade contra a tripanosomíase americana, mas a partir do ano de 2008 uma crescente foi observada, onde de 2008 à 2012, 21 óleos essenciais foram estudados e esses estudos foram compilados em 6 artigos. No período de 2013 a 2018, 11 artigos foram analisados, onde 22 OE foram estudados.

Gráfico 2: Quantidade de óleos essenciais estudados no período de 2002 a 2018, para a doença de Chagas.

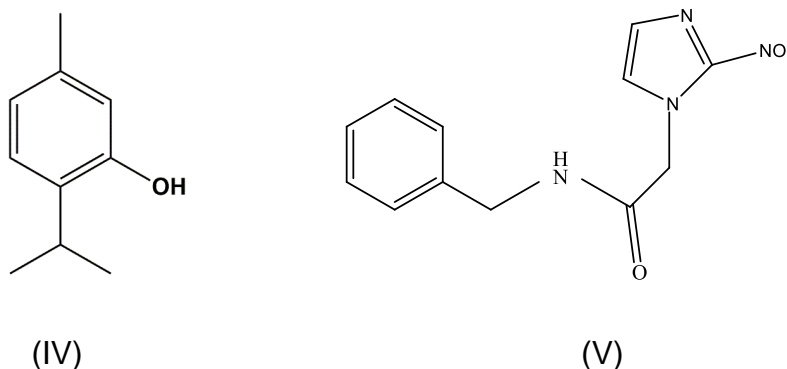


Fonte: Própria autoria

De todos esses estudos, alguns merecem destaque, por ter apresentado uma atividade significativa, com valor de IC_{50} abaixo de $100 \mu\text{g/ml}$ e comparáveis às drogas referência.

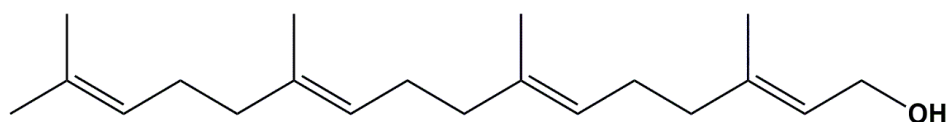
Por exemplo, em 2006, Santoro e colaboradores estudaram a atividade de dois OE obtidos de *Origanum vulgare* e *Thymus vulgaris*, onde o OE de tomilho apresentou valor de $IC_{50}/24\text{h} = 77 \mu\text{g/ml}$ para epimastigotas e $38 \mu\text{g/ml}$ para tripomastigotas. Já o timol (IV) (figura 5), constituinte primário do tomilho apresentou $IC_{50}/24\text{h} = 62 \mu\text{g/ml}$ para epimastigotas e $IC_{50}/24\text{h} = 53 \mu\text{g/ml}$ para tripomastigotas. Ambos mostraram ótimos valores quando comparados a droga de referência benznidazol (V) que seu valor de IC_{50} é aproximadamente $50\mu\text{g/ml}$.

Figura 5: Estrutura química do Timol (IV) e a droga benznidazol (V).



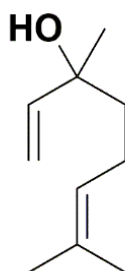
Menna-Barreto em 2008 estudou OE de *Pterodon pubescens*, onde seu extrato etanólico foi subdividido em 3 frações, dos três compostos o diterpeno Geranilgeraniol (figura 6) foi o mais ativo com $IC_{50}/24h = 15.3 \mu g/ml$.

Figura 6: Estrutura química do Geranilgeraniol.



Analisando um estudo mais recente, do ano de 2017, Villamizar e colaboradores analisaram efeito tripanocida do OE de *Piper aduncum* (PaEO), onde o mesmo apresentou como constituintes principais o nerolidol e linalol (figura 7), dentre esses compostos identificados o mais efetivo em inibir o desenvolvimento do *T. cruzi* foi o linalol com $IC_{50}/24h = 306ng/ml$.

Figura 7: Estrutura química do Linalol.

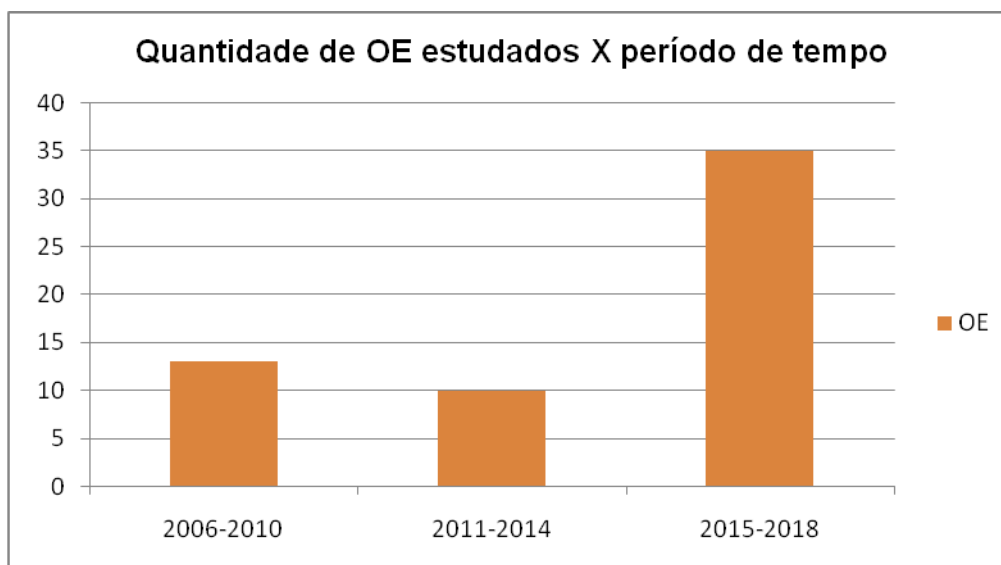


5.2 Doenças do Sono

Os artigos que versam sobre *Trypanosoma brucei* foram obtidos no período de 2006 a 2018, nesses 12 anos foram analisados 58 óleos essenciais de plantas, concentrados em 20 artigos. Percebe-se através do Gráfico 3, que do ano de 2006 a 2010 poucos estudos eram feitos sobre óleos essenciais com atividade contra a tripanosomiase africana, nos anos de 2011 a 2014, pouca importância era dada a essa doença também onde apenas 10 OE foram analisados, mas de 2015 a 2018

uma crescente foi observada, onde nesse período 35 óleos essenciais foram estudados.

Gráfico 3: Quantidade de plantas com óleos essenciais estudados no período de 2006 a 2018, para a doença do sono.

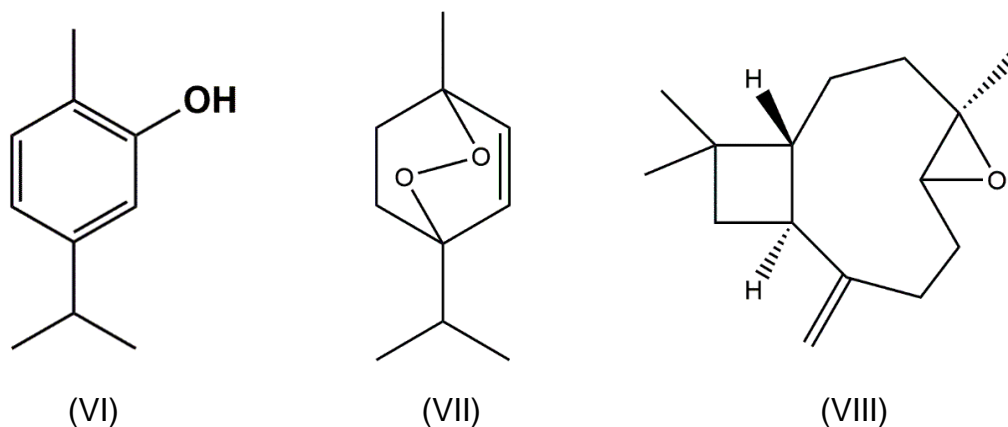


Fonte: Própria autoria

Dentre esses 20 artigos, alguns merecem destaque, por apresentar atividade significativa, com valor de IC_{50} abaixo de $10 \mu\text{g/mL}$ e comparáveis às drogas referência.

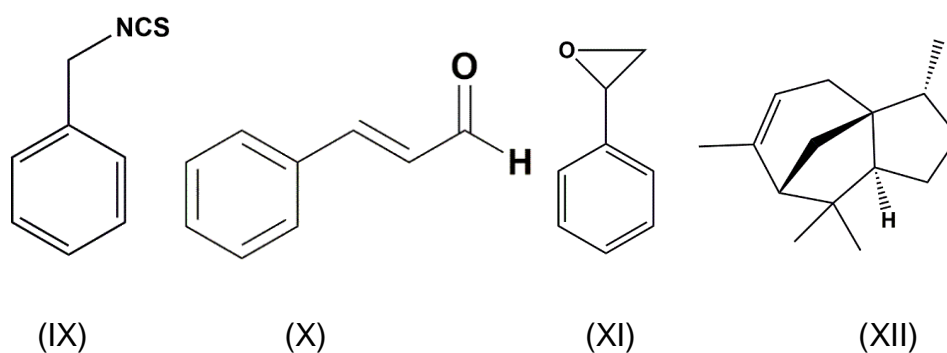
Monzote em 2014 estudou o OE de *Chenopodium ambrosioides L.* (CaEO), onde seus componentes principais são carvacrol (62%) (VI), ascaridol (22%) (VII) e óxido decariofileno (5%) (VIII) (Figura 8) mostraram atividade similar a droga de referência Sumarina, basta comparar os valores de IC_{50} que são bem próximos. Para os componentes principais os valores variaram assim, $IC_{50} = 0.2 \pm 0.07 \mu\text{g/mL}$. Já o IC_{50} da droga de referência é: (IC_{50} de $0.05 \pm 0.05 \mu\text{g/mL}$).

Figura 8: Estruturas químicas do carvacrol (VI), ascaridol (VII) e óxido de cariofileno (VIII)



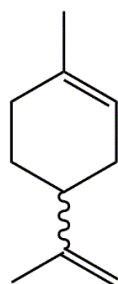
Em 2010, Nibret e seus colaboradores estudaram a atividade contra *T. brucei* de 3 espécies de plantas e seus óleos essenciais foram extraídos em diferentes partes da planta, o OE de *Hagenia abyssinica* foi extraída da flor, o OE de *Leonotisocyc mifolia* extraída das partes aéreas e o OE da *Moringa stenopetala* das sementes. O OE da *Moringa stenopetala* apresentou um melhor valor de IC_{50} e de índice de seletividade (IC_{50} = 5,03 μ g/mL e SI = 2,31). Dos compostos isolados os melhores resultados foram: isotiocianato de benzila (**IX**) (IC_{50} = 1,20 μ g/mL e SI = 3,85), cinamaldeído (**X**) (IC_{50} = 2,93 μ g/mL e SI = 11,13), óxido de estireno (**XI**) (IC_{50} = 3,76 μ g/mL e SI = 19,92) e (-)- α -cedrene (**XII**) (IC_{50} = 4,07 μ g/mL e SI = 5,45) (Figura 9).

Figura 9: Estruturas químicas do isotiocianato de benzila (IX), cinamaldeído (X) óxido de estireno (XI) e (-)- α -cedrene (XII).



Petrelli em 2016 estudou o OE de *Erigeron floribundus* nele continha 85 constituintes e os principais compostos identificados foram sesquiterpenos (60,4%), sendo 38,5% sesquiterpenos oxigenados e 21,9% hidrocarbonetos. O seu componente principal que merece destaque é o limoneno (Figura 10), pois demonstrou uma atividade promissora, com $IC_{50} = 5,6 \pm 1,6 \mu\text{g/mL}$ e $SI \geq 17,85$ e com esses valores ele se torna o principal contribuinte para a potencialidade desse óleo essencial.

Figura 10: Estrutura química do Limoneno.

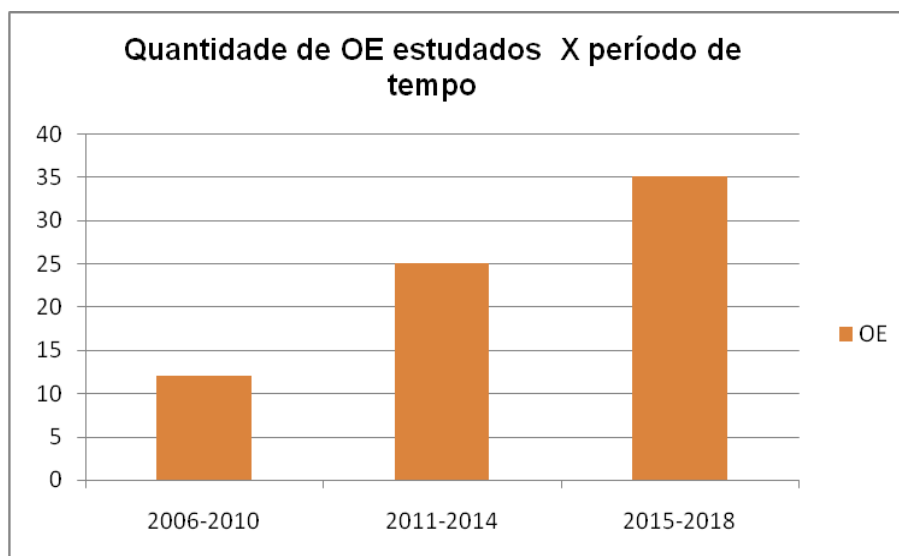


5.3 Leishmaniose

Os artigos que versam sobre leishmaniose foram obtidos no período de 2006 a 2018, nesses 12 anos foram analisados 72 óleos essenciais de plantas, concentrados em 22 artigos. Ao analisar o Gráfico 4, que do ano de 2006 a 2010, apenas 12 plantas foram estudadas com atividade contra leishmaniose, e comparado aos outros anos esse número foi bem reduzido. Nos anos de 2011 a 2014, os valores já foram tendo acréscimo, onde 25 OE de plantas foram analisados, mas de 2015 a 2018 uma crescente foi observada, onde nesse período 35 óleos essenciais foram estudados.

Com isso, percebe-se que no decorrer dos anos os estudos sobre a leishmaniose vem aumentando.

Gráfico 4: Quantidade de plantas com óleos essenciais estudados no período de 2006a 2018, para a Leishmaniose.



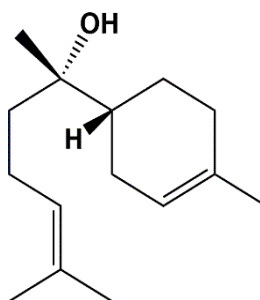
Fonte: Própria autoria

Desses 22 artigos observados, destacam-se 4 por apresentarem alta atividade contra leishmaniose.

Em 2013, Rosa e colaboradores estudaram o efeito leishmanicida de óleos essenciais ricos em linalol e linalol purificado (Figura 7), ambos mostraram atividade potente. Os OEs analisados foram extraídos das folhas do *Croton cajucara*. Os valores de IC_{50} foram 8.3 e 4.3 ng/mL para forma promastigota e os valores de IC_{50} para amastigotas foram 22.0 e 15.5 ng/mL.

Outro estudo também do ano de 2013 estudou o OE de *Vanillos mopsisarbórea*, que apresentou como constituinte principal o α -bisabolol. Esse constituinte inibiu o crescimento da *Leishmania amazonensis* na forma promastigota com valor de IC_{50} foi de 7,35. O α -bisabolol foi mais eficaz contra promastigotas que com amastigotas intracelular e seu índice de seletividade foi $SI=9,38$.

Figura 11: Estrutura química do α -bisabolol.



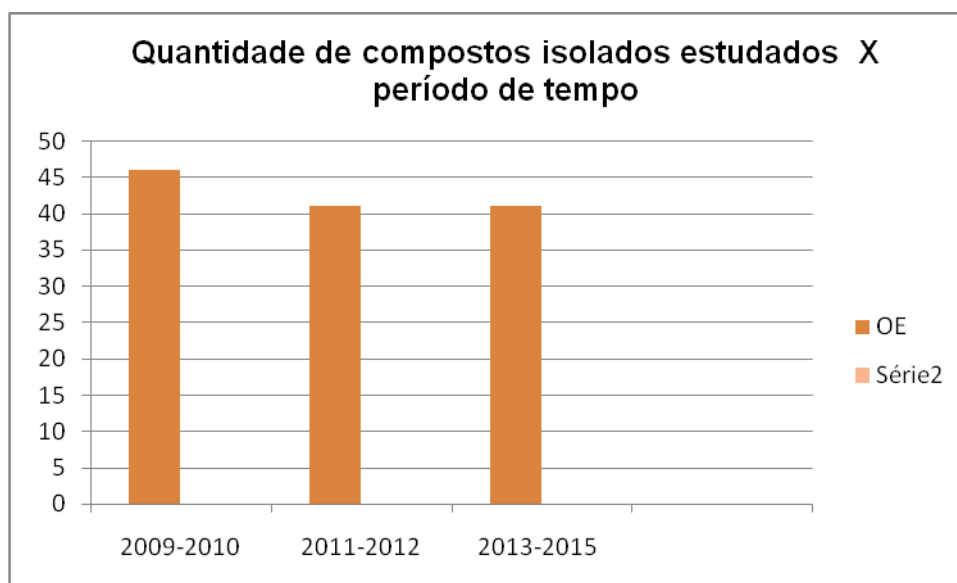
Um artigo mais recente feito por Silva e colaboradores do ano de 2018 foi de grande relevância, foi estudado o OE de *Ocimum canum* Sims que já é utilizado em forma de xarope para tratamento de algumas doenças, mas neste estudo foi estudado de forma específica para a leishmaniose, e ele foi rico em timol, p-cimeno e γ -terpineno. Demonstrou atividade moderada para *Leishmania amazonensis* na forma promastigota (IC_{50} = 17,4mg/ml) e amastigota (IC_{50} = 13,1mg/ml). Esses valores foram mais potentes que a droga de referência, a pentamidina, com valores de SI = 18,1 e 24,0 respectivamente.

5.4 Arbovirose (Dengue)

Os artigos que versam sobre Dengue foram obtidos no período de 2009 a 2015, nesses 6 anos as classes mais estudadas foram os hidrocarbonetos monoterpênicos e monoterpenos oxigenados, em pouca quantidade tinham sesquiterpenos oxigenados, diterpenos, fenilpropanoides, e que as quantidades de compostos estudados para cada classe foram, 15, 41, 2, 1, 13, respectivamente. O Gráfico 5 nos faz perceber, que diferentemente das outras três doenças negligenciadas, a dengue já vem sendo estudada há mais tempo, ela não tomou vez no campo da pesquisa só nos anos mais recentes.

Nos anos de 2009 a 2010, 46 compostos isolados foram estudados e seus respectivos IC_{50} . De 2011 a 2012, 41 compostos foram isolados e estudados, e de 2013 a 2015, também foram estudados 41 compostos. Então se percebe uma homogeneidade nos valores.

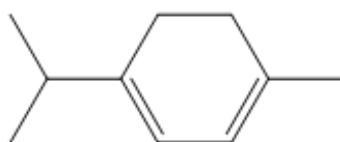
Gráfico 5: Quantidade de compostos isolados estudados no período de 2009 a 2015, para a Dengue.



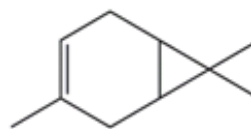
Fonte: Própria autoria

Com esses estudos percebe-se que os compostos isolados mais eficazes foram da classe dos hidrocarbonetos monoterpênicos, dentre eles o α -terpinene (Figura 12 **XIII**) LC_{50} = 14,7 μ g/mL, o limoneno (figura 10) LC_{50} = 18,1 μ g/mL e o 3-careno (Figura 12 **XIV**) LC = 10,7 μ g/mL.

Figura 12: Estrutura química do α -terpinene (XIII) e do 3-careno (XIV).



(XIII)



(XIV)

6 CONCLUSÃO

- As doenças negligenciadas são doenças que acometem mais fortemente populações de baixa renda, em países subdesenvolvidos, por isso o pouco interesse do governo em investir, pois sabe que não terá um retorno lucrativo. Com isso, essas doenças têm ausência de medicamentos, vacinas e os pacientes estão indo a procura de plantas para alcançarem sua cura. Os óleos essenciais são bastante eficientes para cura de doenças, dentre elas as negligenciadas.
- Vários artigos foram revisados com tema principal óleos essenciais para tratamento de doenças negligenciadas, e foi percebido que muito se fazem uso de plantas medicinais, principalmente a população mais pobre, visto a necessidade de tratamento, e pouca opção de drogas. Muitos óleos essenciais já foram identificados que possuem atividade biológica e farmacológica comerciais disponível.
- Das doenças negligenciadas, as que mereceram destaque foram as que acometem fortemente a população brasileira, onde causam inúmeras mortes por ano, dentre elas se destacam: Dengue, doença de Chagas, Leishmaniose. Essas doenças são carentes de tratamento, medicamentos, mas vários estudos já estão sendo feitos para a utilização de óleos essenciais para tratamento dessas doenças.
- A Leishmaniose possui vários estudos promissores, dentre eles o óleo de copaíba, que é rico em sesquiterpenos, e percebeu-se que por isso eram mais ativos. Foram testados em camundongos e obtiveram redução da lesão, mas quando comparado ao medicamento de referencia não houve diferença significativa.
- Ainda sobre a Leishmaniose , foi estudado *Ocimum canun* , e ele foi mais potente que a droga de referencia , sendo rico em monoterpenos. Outro estudo foi sobre *L. infantum* que são fatais para Leishmaniose.
- Outra doença negligenciada são as arboviroses, onde a dengue merece destaque, pois ela é a doença viral mais importante do mundo, não existe tratamento com

remédios para ela. A única forma que existe, é o combate ao seu vetor principal de transmissão, o mosquito *Aedes Aegypti* e uma das formas de combate ao mosquito transmissor da Dengue são os inseticidas (Bti e Termefhos), mas eles possuem desvantagens, pois tem grande toxicidade e não são sustentáveis.

- Com isso, percebe-se a necessidade de novos meios de tratamento, e o método que vem sendo bastante estudado, são os OE, pois apresentam inúmeras vantagens sobre as outras drogas, dentre elas: Baixo custo, baixo teor de alergia, baixa toxicidade.
- A partir desse estudo teórico, chegasse a perspectivas futuras, onde identificamos óleos essenciais ativos para cada uma das doenças negligenciadas analisadas no trabalho, e eles podem servir como protótipos para o desenho ou síntese de compostos com atividades mais promissoras.

REFERÊNCIAS

ALTMANN K.H., GERTSH J. Anticancer drugs from nature-natural products as a unique source of new microtubule-stabilizing agents. *The Royal Society of Chemistry*, vol. 24, 327-357, 2007.

ASSIS S. S. D. AND ARAUJO-JORGE T. C., “O que dizem as propostas curriculares do Brasil sobre o tema saúde e as doenças negligenciadas?: aportes para a educação em saúde no ensino de ciências,” *Ciência & Educação*, vol. 24, no. 1, 125–140, 2018.

BADKE M. R., BUDÓ M. D. L. D., SILVA F. M. D., RESSEL, L. B. Plantas medicinais: o saber sustentado na prática do cotidiano popular. *Esc Anna Nery*, vol. 15, no. 1, 132-139, 2011.

BAKKALI, F.; AVERBECK, S .; AVERBECK, D .; IDAOMAR, efeitos Biológicos de óleos essenciais-um comentário. *Chem alimentos. Toxico*.vol. 46, 446-75, 2008.

CHABNER, B.A., BRUNTON, L.L. *Goodman & Gilman's the pharmacological basis of therapeutics*. Nova Iorque, McGraw-Hill, 11ª edição, 1315–1403, 2005.

CRAGG, G. M.. PACLITAXEL (TAXOL): A success story with valuable lessons for natural product drug discovery and development. *Medical Research Review*, vol. 18, no. 5, 315–331, 1998.

CORDELL GA. *Introduction to alkaloids: a biogenetic approach*. Nova York: John-Wiley & Sons,. 208, 1981.

CROTEAU R, KUTCHAN TM, LEWIS NG 2000, Natural Products (Secondary Metabolites). In: Buchanan B., Grissem W., Jones R. (Eds.) *Biochemistry & Molecular Biology of Plants*, Rockville: American Society of Plant Physiologists, 1250-1318.

DIAS C. N. and MORAES D. F. C., "Essential oils and their compounds as *Aedes aegypti* L. (Diptera Culicidae) larvicides: review," *Parasitology Research*, vol. 113, no. 2, 565–592, 2014.

FÉLIX M. B., SOUZA E. R., LIMA M. D. C. A. ET AL., "Antileishmanial activity of new thiophene-indole hybrids: design, synthesis biological and cytotoxic evaluation, and chemometric studies," *Bioorganic & Medicinal Chemistry*, vol. 24, no. 18, 3972–3977, 2016.

GAUTAM N, MANTHA AK, MITTAL S. Essential oils and their constituents as anticancer agents: a mechanistic view. *Biomed. Res.* 1-23, 2014.

HARBORNE JB. *Introduction to ecological biochemistry*. London: Academic Press, 1988.

HEIL, M.; BAUMANN, B.; ANDARY, C.; LINSENMAIR, K. E; MCKEY, D. Extraction and quantification of "condensed tannins" as a measure of plant anti-herbivore defence? Revisiting an old problem. *Naturwissenschaften*. vol.89, 519-524, 2002.

JACK D.B. One hundred years of aspirin. *Lancet* 350 (9075), 437–439, 1997.

JENNEWEIN, S., CROTEAU, R. Taxol: biosynthesis, molecular genetics, and biotechnological applications. *Applied Microbial Biotechnology*, vol.57, 13-19, 2001.

KRAITZER, A. ET AL. Mechanisms of antiproliferative drug release from bioresorbable porous structures. *Journal of Biomedical Research*. Part, vol.101, no 5, 1302-1310, 2012.

KATSUNO K., BURROWS J. N., DUNCAN K. ET AL., "Hit and lead criteria in drug discovery for infectious diseases of the developing world," *Nature Reviews Drug Discovery*, vol. 14, no. 11, 751–758, 2015.

LÉVESQUE H., LAFONT O.. Aspirin throughout the ages: an historical review. *Rev Med. Interne*. vol.1, 8-17, 2000.

LEROUX H.. Discovery of salicine historique. Rev. Med. Interne 21 (Suppl. 1), 8s–17s.. J. Chim. Med. Vol. 6, 340–432,1830.

LIMA-CAMARA T. Arboviroses emergentes e novos desafios para a saúde pública no brasil. *Rev Saúde Pública*; vol. 50, 36, 2016.

LORENZO, D., GONZALEZ, G., ROSSINI C. Farmacognosia y productos naturales. Contenido del curso teórico, Apostila 04: Aceites Esenciales. Universidad de la Republica do Uruguay. Montevideo, 14-18, 2002.

LUNA, Emanuela. Active Essential Oils and Their Components in Use against Neglected Diseases and Arboviruses, *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 6587150 , 1-52, 2019

MAHBOUB, M.; KHAMECHIAN, T.; KAZEMPOUR, N. Total phenolic and flavonoids content, antioxidant and antimicrobial activities of aziliaeryngioides extracts. *Journal of Biologically Active Products from Nature*, vol. 2, no. 3, 144- 150, 2013.

MAFFEI ME. Sites of synthesis, biochemistry and functional role of plant volatiles. *S. Afr. J. Bot.* ,vol.76, no 4, 612–631, 2010.

MENEZES PMN, BRITO MC, LUCCHESI AM, LIMA JT, RIBEIRO LAA, SILVA FS, atividade farmacológica de óleos essenciais no sistema respiratório: uma revisão sistemática de estudos pré-clínicos ,*Rev. Eletr. Farm.*, Goiânia, vol. 14, no. 3, 16-31, 2017.

MELLO, J. C.P.; SANTOS, S. C. TANINOS. IN: SIMÕES, C.M.; SCHENKEL, E. P.; GOSMANN, G.; MELLO, J. C.P.; MENTZ, L.A.; PETROVICK, P.R. Farmacognosia: da planta ao medicamento. 3 ed. Porto Alegre: Ed.UFGRS/Ed.UFSC. cap. 24, 517-543, 2001.

MENDONÇA JUNIOR F. J. B., “Chapter 1: “As doenças negligenciadas e seu contexto no Brasil”,” in *Doenças Negligenciadas Sob a ótica da Química Medicinal*, 11–26, CRV, Curitiba/- Parana, Brazil, 1st edition edition, 2015.

MINISTÉRIO DA SAÚDE (BR). Programa Nacional de Plantas Mediciniais e Fitoterápicos. [on-line]. 2007; [citado 2009 20 mar]; Disponível em: http://portal.saude.gov.br/portal/arquivos/pdf/politica_plantas_mediciniais_fitoterapia.pdf>

MOREL CM. Inovação em saúde e doenças negligenciadas (Editorial). *Cad Saude Publica*; vol. 22, no.8, 1522- 1523, 2006.

NAVARRO D., SILVA P., SILVA M., NAPOLEAO T. AND PAIVA P. "Larvicidal activity of plant and algae extracts, essential oils and isolated chemical constituents against *Aedes aegypti*," *The Natural Products Journal*, vol. 3, no. 4, 268–291, 2014.

NOBILI, S. ET AL.. Natural compounds for cancer treatment and prevention. *Pharmacological Research*, vol.59, 365-378, 2009.

NIKOLAY B., MWANDAWIRO C. S., KIHARA J. H. ET AL., "Understanding heterogeneity in the impact of national neglected tropical disease control programmes: evidence from school-based deworming in Kenya," *PLOS Neglected Tropical Diseases*, vol. 9, no. 9, article e0004108, 2015.

NUNN J.F. *Ancient egyptian medicine*. London: British Museum Press, p. 158, 1996.

PAN, L., CHAI, H., KINGSTON, D. The continuing search for antitumor agents from higher plants. *Phytochemistry Letters*, vol 3, no. 1, 1-8, 2009.

PERES, L. E. P.. *Metabolismo Secundário*. Piracicaba – São Paulo: Escola Superior de Agricultura Luiz de Queiroz. ESALQ/USP, 1-10, 2004.

RIDDLE J.M.. Historical data as an aid in pharmaceutical prospecting and drug safety determination. *J. Altern. Complement. Med.* Vol. 5, no.2, 195-201, 1999.

RAINFORD K.D.. *Aspirin And The Salicylates*. London: Butterworths, 1944.

SAMPATH,A.; PADMANABHAN, R. Molecular targets for flavivirus drug Discovery. Antiviral Res. vol.81,6-15,2009.

SANTOS, AS; ALVES, SM; FIGUEIREDO, FJC; NETO, Ogr descrição de sistema e de métodos de extração de óleos essenciais e determinação de umidade de biomassa em laboratório. 1-6, 2004.

SANGWAN N.S., FAROOQI A.H.A., SHABIH F. SANGWAN R.S. Regulation Of Essential Oil Production In Plants. Plant Growth Regulation. vol. 34, 3–21, 2001.

STEVENS A.J.; GAHAN, M.E.; MAHALINGAM, S.; KELLER, P.A. The Medicinal Chemistry of Dengue Fever J. Med. Chem., vol.52,no.24, 7911-7926,2009.

SRITABUTRA D., SOONWERA M., WALTANACHANOBON S., AND POUNGJAI S., “Evaluation of herbal essential oil as repellents against *Aedes aegypti* (L.) and *Anopheles dirus* Peyton & Harrison,” Asian Pacific Journal of Tropical Biomedicine, vol. 1, no. 1, 124–128, 2011.

SIMÕES O.C.M; SPITZER, V .; SCHENKEL P.E; GOSMANN, G .; MELLO J.C.P; MENTZ L.A; PETROVICK, pr Farmacognosia: da planta ao medicamentos; 5 rd Ed. UFSC: Porto Alegre, 2004.

SIMÕES, C.M.; SCHENKEL, E. P.;GOSMANN, G.; MELLO, J. C.P.; MENTZ, L.A.; PETROVICK, P. R. Farmacognosia: Da Planta Ao Medicamento .3 ed. Porto Alegre: Ed. UFRGS/Ed. UFSC, cap.27, 597-619, 2001.

UNIYAL A., TIKAR S. N., SINGH R., ET AL., “Synergic effect of effective oils against *Aedes aegypti* female mosquito, vector od dengue and chikungunya,” International Journal of Mosquito Research, vol. 2, no. 4, 29–35, 2015.

VANCLEEF, K.W.R.; OVERHEUL, G.J.; THOMASSEN,M.C.; KAPTEIN, S.E.J.F.; DAVIDSON.A.D; JACOBS, M.; NEYTS,J.; VAN KUPPEVELD, F.J.M.; VAM RIJ,R.P.

Identification of a new dengue virus inhibitor that targets the viral NS4B protein and restricts genomic RNA replication, *Anti-viral Res.*, vol.99, P. 165-171, 2013.

WALL, M. E., WANI, M. C.. Camptothecin And Taxol: From Discovery To Clinic. *Journal of Ethnopharmacology*, vol.51, 239-254, 1996.

World Health Organization (WHO). *Global Plan To Combat Neglected Tropical Diseases 2008-2015*. Geneva: WHO; 2007

WHO/Department of control of neglected tropical diseases, *Sustaining the Drive to Overcome the Global Impact of Neglected Tropical Diseases: Second WHO Report on Neglected Diseases*, WHO, Geneva, Switzerland, 2012.

WHO, *First WHO Report Neglected Tropical Diseases: Working to Overcome the Global Impact Neglected Tropical Diseases*, WHO/HTMA/NTD/2010, Geneva, Switzerland, http://www.who.int/neglected_diseases/2010report/en/, 2018.

WHO. Global alert and response (GAR). Dengue/dengue haemorrhagic fever. Disponível em : <[http:// www.who.int/csr/disease/dengue/en/index](http://www.who.int/csr/disease/dengue/en/index.html). Html>. Acesso em novembro de 2018.

YAZBEK M. C., “Pobreza no Brasil contemporâneo e formas de seu enfrentamento,” *Serviço Social & Sociedade*, vol. 110, no. 110, 288–322, 2012.





ZHU B.C.R, HENDERSON G., CHEN F., FEI H., LAINE R.A. Evaluation of Vetiver Oil and Seven Insect-Active Essential oils Against The Formosan Subterranean Termite. *J Chem. Ecol.* vol.27: 1617-1625, 2001.

ZHU, S., X. C. LIU, Z. L. LIU, AND X. XU, “Chemical composition of *Salvia plebeian* R. Br. Essential oil and its larvicidal activity against *Aedes aegypti* L.,” *Tropical Journal of Pharmaceutical Research*, vol. 14, no. 5, 831–836, 2015.

APÊNDICE A – (PRODUÇÃO CIENTÍFICA)

Review Article

Active Essential Oils and Their Components in Use against Neglected Diseases and Arboviruses

Emanuela Coutinho Luna,¹ Isadora Silva Luna,¹ Luciana Scotti ,^{2,3} Alex France M. Monteiro,³ Marcus Tullius Scotti ,³ Ricardo Olímpio de Moura,¹ Rodrigo Santos Aquino de Araújo ,¹ Kadja Luana Chagas Monteiro,⁴ Thiago Mendonça de Aquino,⁵ Frederico Fávaro Ribeiro,¹ and Francisco Jaime Bezerra Mendonça Junior ¹

¹Laboratório de Síntese e Vetorização de Moléculas, Departamento de Ciências Biológicas, Universidade Estadual da Paraíba, 58071-160 João Pessoa-PB, Brazil

²Teaching and Research Management-University Hospital, Federal University of Paraíba, Campus I, João Pessoa-PB, Brazil

³Postgraduate Program in Natural Products and Synthetic Bioactive, Federal University of Paraíba, Campus I, João Pessoa-PB, Brazil

⁴Laboratory of Medicinal Chemistry, Nursing and Pharmacy School, Federal University of Alagoas, 57072-900 Maceió-AL, Brazil

⁵Chemistry and Biotechnology Institute, Federal University of Alagoas, Maceió, Brazil

Correspondence should be addressed to Francisco Jaime Bezerra Mendonça Junior; franciscojbmendonca@yahoo.com.br

Received 26 June 2018; Accepted 6 November 2018; Published 7 February 2019

Academic Editor: Ryoji Nagai

Copyright © 2019 Emanuela Coutinho Luna et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The term *neglected diseases* refers to a group of infections caused by various classes of pathogens, including protozoa, viruses, bacteria, and helminths, most often affecting impoverished populations without adequate sanitation living in close contact with infectious vectors and domestic animals. The fact that these diseases were historically not considered priorities for pharmaceutical companies made the available treatments options obsolete, precarious, outdated, and in some cases nonexistent. The use of plants for medicinal, religious, and cosmetic purposes has a history dating back to the emergence of humanity. One of the principal fractions of chemical substances found in plants are essential oils (EOs). EOs consist of a mixture of volatile and hydrophobic secondary metabolites with marked odors, composed primarily of terpenes and phenylpropanoids. They have great commercial value and were widely used in traditional medicine, by phytotherapy practitioners, and in public health services for the treatment of several conditions, including neglected diseases. In addition to the recognized cytoprotective and antioxidative activities of many of these compounds, larvicidal, insecticidal, and antiparasitic activities have been associated with the induction of oxidative stress in parasites, increasing levels of nitric oxide in the infected host, reducing parasite resistance to reactive oxygen species, and increasing lipid peroxidation, ultimately leading to serious damage to cell membranes. The hydrophobicity of these compounds also allows them to cross the membranes of parasites as well as the blood-brain barrier, collaborating in combat at the second stage of several of these infections. Based on these considerations, the aim of this review was to present an update of the potential of EOs, their fractions, and their chemical constituents, against some neglected diseases, including American and African trypanosomiasis, leishmaniasis, and arboviruses, specially dengue.

1. Introduction

Neglected diseases (ND) are a group of infections caused by various classes of infectious and parasitic pathogens, including protozoa, viruses, bacteria, and helminths. They most

often affect low-income populations, with higher prevalence in tropical and subtropical countries. According to the World Health Organization (WHO), they are a set of 17 diseases, including leishmaniasis, African and American trypanosomiasis, leprosy, tuberculosis, leptospirosis, onchocerciasis,

and schistosomiasis, affecting more than one billion people around the world and considered a threat to public health in 149 countries [1, 2].

The fact that these diseases are not considered priorities by large medical and pharmaceutical companies results in low investment in research and development of new drugs, causing the few available treatment options to become obsolete, precarious, outdated, and even in some cases nonexistent [3].

These diseases are known for the lack of attention paid to them by political, social, and health entities. The worsening of social and health conditions in a great part of the world's population has accelerated in recent years according to studies providing data regarding current social policies [4–6].

According to some studies in Latin American countries, Brazil has the highest rate of neglected diseases, and a large part of the Brazilian population both above and below the poverty line suffers from some of these diseases [7–9].

Several neglected diseases are arboviruses, that is, viral diseases transmitted through the saliva of contaminated arthropods [10]. Thus, they spread with worrisome epidemiological speed because of human exposure to the insect vectors [11, 12]. In some cases, a single vector can transmit more than one disease, as is the case of the vector *Aedes aegypti* that may transmit dengue, Zika, and chikungunya.

According to some authors [13, 14], 80% of the Brazilian population lives in urban areas. Demographic expansion and climatic conditions create an attractive environment for the reproduction of arbovirus vectors, rapidly affecting a large part of the population living in these urban centers [13]. Due to the absence of many natural predators, disease-bearing arthropods reproduce more easily in urban centers.

The use of plants for medicinal, religious, and cosmetic purposes dates back to the emergence of humanity. This historical interest promoted the development of several areas of inquiry invested in understanding and unraveling the potential of substances produced by plants as a result of their adaptive evolution [15, 16].

One of the principal fractions of chemical substances found in plants are essential oils (EOs). EOs consist primarily of a mixture of volatile hydrophobic secondary metabolites with marked odors and great commercial value; EOs may be thought of as fingerprints of the plants where they are found [17, 18]. They include aromatic alcohols, acids, esters, phenolics, ketones, aldehydes, and hydrocarbons. In plants, EOs act as protective agents against predators and attractants for pollinators [19, 20].

The main chemical compounds found in EOs are terpenoids and phenylpropanoids [21, 22] that are widely used as bioactive molecules in biology, agronomy, medicine, and pharmaceutical sciences. Among the medical-pharmaceutical activities of these compounds are antitumor, antihelminthic, and larvicidal [23–25] and insecticidal [26–32] activities, as well as activity against arbovirus vectors [33, 34].

Despite the recognized cytoprotective and antioxidative activities of these compounds, in many cases larvicidal, insecticidal, and antiparasitic activities are associated with the induction of oxidative stress in the parasite, increasing the level of nitric oxide production by the infected host, reducing

parasite resistance to reactive oxygen species, and generating high levels of free radicals and increasing lipid peroxidation, ultimately leading to serious damage to cell membranes and the killing of parasites [35–40].

Based on these considerations, in this review an update of the potential of EOs, their fractions, and their components that are active against some neglected diseases, including American and African trypanosomiasis, leishmaniasis, and arboviruses, specially dengue is presented.

To compose the database, the authors did a systematical search in the following databases: PubMed, Web of Science, Medline, SciELO, Cochrane Library, and NAPRALERT. The following search terms were combined and screened: essential oils, name of the neglected disease, and/or the parasite name. No language restrictions were applied. The period considered was the last 10 years, without however disregarding some articles of revision, and some classical literatures were considered important.

1.1. Essentials Oils Active against Trypanosoma cruzi. Chagas disease (CD), also known as American trypanosomiasis, is a potentially life-threatening disease caused by the protozoan *Trypanosoma cruzi* [41]. According to the World Health Organization, CD affects about 7 million people worldwide and is endemic in 21 Latin American countries. It is estimated that CD leads to more than 7000 deaths per year and there are about 25 million people at risk for infection. Transmission to humans usually occurs through the excrement of infected vector insects (haematophagous triatomines) that normally become active at night, feeding on mammalian blood by biting exposed skin and defecating close to the bite. Transmission can also occur through transfusion of infected blood, congenital transmission, and (less frequently) organ transplantation or laboratory accidents [42].

Although it is an infectious disease with more than 100 years since its discovery, the morbidity and mortality associated with CD remains high. This may be attributed to several factors, including the absence of effective vaccines and/or medical treatments. Currently, only two drugs are available for CD treatment: benznidazole (BZ) and nifurtimox (NFX). Unfortunately, these drugs carry high toxicity and cause severe side effects that often interrupt treatment [43]. Therefore, there is a need for new therapeutic alternatives for CD that are more effective and less toxic for both acute and chronic phases.

Therefore, the use of natural products is an important strategy to identify new trypanocidal compounds, and the literature already described promising studies with the use of EOs, found in some species of plants in many tropical countries [44].

Over the last two decades, the trypanocidal activity of approximately 400 plant species has been analyzed; however, few reports have assessed the trypanocidal activity of EOs [45, 46].

The literature described that EOs have been used since the Middle Ages by Arabs for their antiseptic, bactericidal, virucidal, and fungicidal properties. They are also used for embalming and preservation of foods and as drugs with

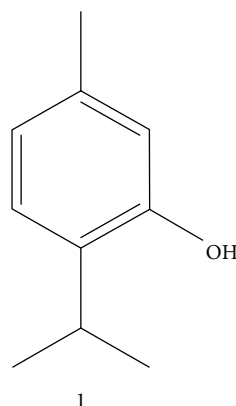


FIGURE 1: Chemical structure of thymol (1) - the main component of *T. vulgaris* EO.

antimicrobial, analgesic, sedative, anti-inflammatory, spasmolytic, and local anesthetic properties [47]. However, little was known about their antiparasitic applications, with the first reports appearing only at the end of the 20th century and beginning of the 21st century. Chagas disease was no different, and only in recent decades has there been an increase in the number of publications describing the use of EOs and/or their constituents with inhibitory activity against trypanosomatid protozoa [48–50].

Holetz and coworkers produced one of the first reports of the effects of the essential oil of *Ocimum gratissimum* on *Herpetomonas samuelpessoai*, a nonpathogenic trypanosomatid that shares important antigens with *T. cruzi* and can be easily cultured. This trypanosomatid also induced humoral and cell-mediated immune responses, showing itself to be a good model for study of the biology of trypanosomatids and a suitable model for screening new trypanocidal drugs. The EO of *Ocimum gratissimum* inhibited protozoal growth in a dose-dependent manner with IC₅₀ values between 100 and 91 µg/mL, at concentrations from 20 to 250 µg/mL [51, 52].

In 2006, Santoro and colleagues investigated the effects of EOs from *Origanum vulgare* and *Thymus vulgaris* on growth and ultrastructure of evolutionary forms of *T. cruzi*. EO from oregano showed an IC₅₀/24 h value of 175 µg/mL against epimastigotes and induced trypomastigote lysis with IC₅₀/24 h of 115 µg/mL. Thyme EO presented an IC₅₀/24 h of 77 µg/mL for epimastigotes and 38 µg/mL for trypomastigotes. Thymol (1) (Figure 1), the primary constituent of thyme, was also tested and showed an IC₅₀/24 h value of 62 µg/mL for epimastigotes and an IC₅₀/24 h value of 53 µg/mL for trypomastigotes. These IC₅₀/24 h results were similar to those obtained after treatment *in vitro* of the parasites with the reference drug benznidazole (BZ) (IC₅₀/24 h approximately 50 µg/mL) [53].

In another study, the Santoro group evaluated the EOs of three species, clove (*Syzygium aromaticum* L.), basil (*Ocimum basilicum* L.), and yarrow (*Achillea millefolium* L.) and some of their primary constituents (eugenol (2) and linalool (3)) (Figure 2). Treatment with EOs and their

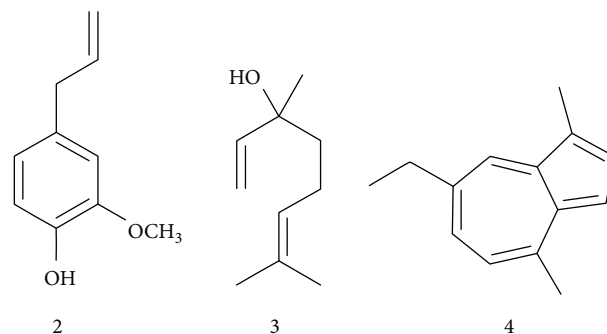


FIGURE 2: Chemical structures of eugenol (2), linalool (3), and chamazulene (4) - main constituents of clove (*Syzygium aromaticum* L.), basil (*Ocimum basilicum* L.), and yarrow (*Achillea millefolium* L.).

constituents showed that they inhibited *T. cruzi* growth, with clove EO being the most effective. Its IC₅₀/24 h value was 99.5 µg/mL for epimastigotes and 57.5 µg/mL for trypomastigotes. Incubation of *T. cruzi* with eugenol (2) (the main constituent of clove) gave an IC₅₀/24 h value of 246 µg/mL for epimastigotes and 76 µg/mL for trypomastigotes. This suggested that the chemical constituents of clove EO had a synergistic effect that increased trypanocidal activity. Linalool (3) (the primary constituent of basil) was also tested and gave IC₅₀/24 h values of 162.5 µg/mL for epimastigotes and 264 µg/mL for trypomastigotes. Chamazulene (4) (Figure 2), one of the primary constituents of yarrow EO, was not evaluated in their study [54].

Menna-Barreto and coworkers evaluated the potential trypanocidal effect of the oleaginous ethanolic extract of *Pterodon pubescens* seeds, its fractions, and geranylgeraniol, among other components isolated from the hexane fraction. The ethanolic extract was fractionated, yielding three sub-fractions including geranylgeraniol (5) (Figure 3). The EO of *P. pubescens*, its fractions, and geranylgeranyl induced dose-dependent lysis in *T. cruzi* trypomastigotes. Geranylgeraniol (5) was the most active compound, with an IC₅₀/24 h value of 15.3 µg/mL [55].

Escobar and coworkers evaluated the antiprotozoal activities of Colombian *Lippia* spp. EO and their major components. Nineteen EO samples were extracted from the aerial parts of five different species by microwave radiation-assisted hydrodistillation and were characterized by GC-FID and gas chromatography–mass spectrometry (GC-MS). Geraniol (6), neral (7), limonene (8), nerol (9), carvacrol (10), *p*-cymene (11), γ -terpenes (12), carvone (13), and thymol (1) were major components identified. Nine oils were active against epimastigotes from *T. cruzi* with IC₅₀ values in the range of 5.5 to 32.2 µg/mL. Six EOs were active against amastigotes interiorized in Vero cells with IC₅₀ ranging from 12.2 to 53.0 µg/mL. In addition, the authors evaluated seven of the major EO components, including thymol (1), carvacrol (10), geraniol, and *p*-cymene (11) (Figure 4) which were active against epimastigotes, with IC₅₀ values ranging from 0.3 to 28.1 µg/mL. Thymol (1) and *S*-carvone (13) were the

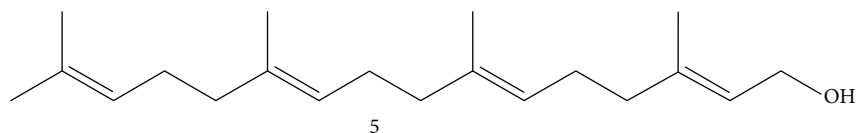


FIGURE 3: Chemical structure of geranylgeraniol, one of the main components of the ethanolic extract of *Pterodon pubescens* seeds.

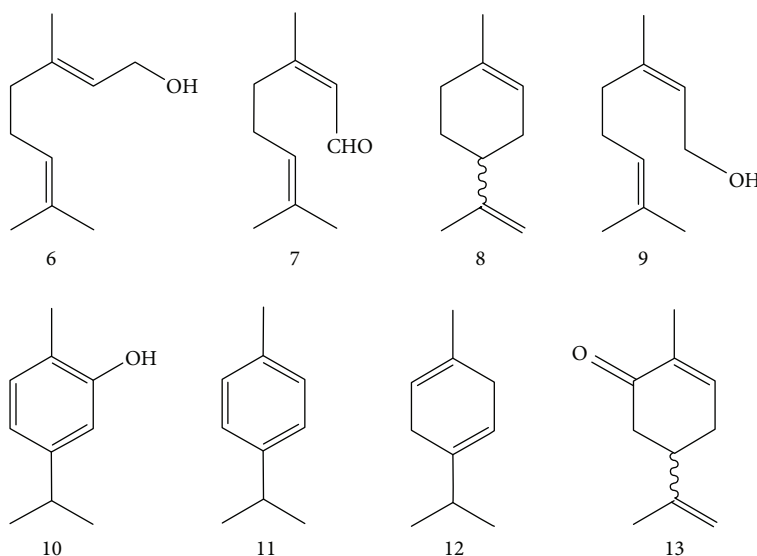


FIGURE 4: Chemical structures of carvacrol (10), geraniol (6), *p*-cymene (11), and other terpenes from Colombian *Lippia* spp. EO.

most active against intracellular amastigote-infected Vero cells, with IC_{50} values of 3.6 and 6.0 $\mu\text{g}/\text{mL}$, respectively [56].

In a study by Rojas and coworkers, the authors evaluated the *in vitro* activity of EOS from 10 plants against *T. cruzi*, their cytotoxic activities, and their modulatory activities in a nitric oxide assay. The evaluated plants were *Mentha piperita* L. (mentha), *Rosmarinus officinalis* L. (romero), *Chenopodium ambrosioides* L. (paico), *Eucalyptus globulus* Labill (eucalipto), *Artemisia absinthium* L. (ajenjo), *Melissa officinalis* L. (toronjil), *Minthostachys setosa* Brig (muña), *Cymbopogon citratus* (hierba luisa), *Aloysia triphylla* (cedrón), and *Mentha spicata* L. (hierba buena). Of these, EOS from *Cymbopogon citratus* and *Aloysia triphylla* were the most active against epimastigote forms, inhibiting *T. cruzi* growth with IC_{50} values of 63.09 and 96.49 $\mu\text{g}/\text{mL}$, respectively. There was no significant variation in the concentration of nitric oxide, and no cytotoxicity was evident [57].

Rojas and colleagues also evaluated the *in vivo* anti-*T. cruzi* effects of *Cymbopogon citratus* and *Aloysia triphylla* EOS in Balb/c mice. *C. citratus* EO administered at 250 mg/kg/day reduced parasitemia peaks from 113.92 ± 25.66 to 74.60 ± 12.37 trypomastigotes/mL. Reduction in the number of amastigotes and number of inflammatory infiltrates in the heart was also observed. When administered at 100 mg/kg/day, no reduction in the number of trypomastigotes was observed (77.40 ± 14.93 trypomastigotes/mL) [58]. *Aloysia triphylla* EO produced significant reduction in parasitemia (85.4%) with a peak of 250 mg/kg/day. They also

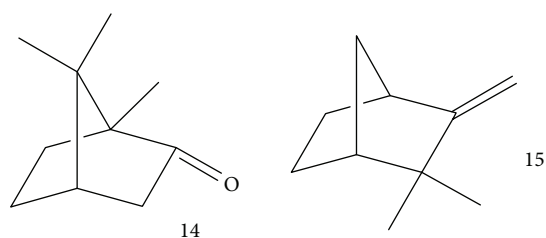


FIGURE 5: Chemical structure of camphor (14) and camphene (15), the main constituents of *Piper malacophyllum* EO.

observed a reduction in the number of amastigotes and inflammatory infiltrates in the heart [59].

Santos et al. evaluated *Piper malacophyllum* EO against diverse microorganisms including *T. cruzi*. Among the 28 compounds identified in the EO, (+) camphor (14) was the major constituent (32.8%) followed by camphene (15) (17.8%) (Figure 5). *P. malacophyllum* EO showed activity against epimastigote forms of *T. cruzi* with an IC_{50} value of 311.82 $\mu\text{g}/\text{mL}$. This was considered a low activity value compared to that of other EOS described in the literature [60].

EOS from *Lippia sidoides*, *Lippia origanoides*, *Chenopodium ambrosioides*, *Ocimum gratissimum*, *Justicia pectoralis*, and *Vitex agnus-castus* were tested against *T. cruzi* by Borges and coworkers. All EOS inhibited epimastigote growth and reduced cell viability of trypomastigote forms in a dose-dependent manner. *C. ambrosioides* (main constituent – terpinolene (16) (69.9%)), *L. origanoides*

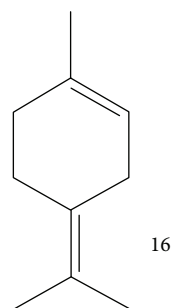


FIGURE 6: Chemical structure of terpinolene (**16**) - main constituent isolated from *Chenopodium ambrosioides* EO.

(main constituent – carvacrol (**10**) (37.3%)), and *L. sidoides* (main constituent – thymol (**1**) (78.4%)) (Figures 1, 4, and 6) were the most effective against epimastigote forms (IC_{50} values of 21.3, 26.2, and 28.9 $\mu\text{g/mL}$, respectively). The less active were EOs obtained from *J. pectorales*, *O. gratissimum*, and *V. agnus-castus* with IC_{50} values of 56.8, 71.1, and 157.1 $\mu\text{g/mL}$, respectively. On the other hand, *L. sidoides*, *O. gratissimum* (38.4% – eugenol (**2**) as the main constituent), *C. ambrosioides*, and *L. origanoides* were found to be more effective against trypomastigotes with $LC_{50}/24\text{h}$ values of 10.3, 11.5, 28.1, and 39.7 $\mu\text{g/mL}$, respectively [61].

Esperandim et al. investigated the activity *in vitro* of the *Piper cubeba* EO against trypomastigote and amastigote forms of *T. cruzi* and promastigote forms of *Leishmania amazonensis*. GC-MS analysis of the essential oils demonstrated that the main components were sabinene (**17**) (19.99%), eucalyptol (**18**) (11.87%), γ -terpineol (**19**) (6.36%), α -pinene (**20**) (5.82%), and camphor (**14**) (5.61%) (Figure 7). The *in vitro* activity against trypomastigotes and amastigotes of *T. cruzi* increased with increasing concentrations, giving IC_{50} values of 45.5 and 87.9 $\mu\text{g/mL}$, respectively. The EO was not active against *L. amazonensis* [62].

In 2014, Azeredo and coworkers evaluated the *in vitro* antitrypanocidal activity of eight different EOs (*Cinnamomum verum*, *Citrus limon*, *Cymbopogon nardus*, *Corymbia citriodora*, *Eucalyptus globulus*, *Eugenia uniflora*, *Myrocarpus frondosus*, and *Rosmarinus officinalis*) against *T. cruzi*. Of these, *Cinnamomum verum* EO was the most effective against *T. cruzi* epimastigotes ($IC_{50}/24\text{h} = 24.13\ \mu\text{g/mL}$), followed by *Myrocarpus frondosus* ($IC_{50}/24\text{h} = 60.87\ \mu\text{g/mL}$) and *Eugenia uniflora* ($IC_{50}/24\text{h} = 70\ \mu\text{g/mL}$). No other evaluated EOs presented significant activity. In addition, *C. verum* EO showed $IC_{50}/24\text{h}$ values of 5.05 $\mu\text{g/mL}$ and 20 $\mu\text{g/mL}$ against *T. cruzi* metacyclic trypomastigotes and intracellular amastigotes, respectively. GC-MS analysis of *C. verum* EO showed (*E*)-cinnamaldehyde (**21**) (81.52%) (Figure 8) and eugenol (**2**) (16.68%) as the main components [63].

Monzote and colleagues evaluated the *Chenopodium ambrosioides* EOs and their principal components against *Leishmania infantum*, *Plasmodium falciparum*, *Trypanosoma brucei*, and *T. cruzi*. *C. ambrosioides* EO showed activity against evaluated protozoa, with IC_{50} values ranging

between 0.2 and 6.4 $\mu\text{g/mL}$. Against *T. cruzi*, the IC_{50} value was 1.9 $\mu\text{g/mL}$ [64].

In 2015, Andrade et al. evaluated the trypanocidal activity of EOs from *Cinnamodendron dinisii* Schwacke (canellaceae) and *Siparuna guianensis* Aublet (Siparunaceae). Both EOs showed low trypanocidal activity, with $IC_{50}/24\text{h}$ values of 209.30 $\mu\text{g/mL}$ for *S. guianensis* and 282.93 $\mu\text{g/mL}$ for *C. dinisii*. The $IC_{50}/24\text{h}$ of the reference drug benznidazol was 12.8 $\mu\text{g/mL}$ [65].

The EO from *Latana camara* leaves was tested against *Leishmania braziliensis* and *T. cruzi* by Barros and coworkers. They found that *L. camara* EO was more effective against *L. braziliensis* than *T. cruzi* with IC_{50} values of 72.31 and 201.94 $\mu\text{g/mL}$ to promastigote and epimastigote forms, respectively. The authors also evaluated the composition of this EO by CG-MS and found that the main constituents were (*E*)-caryophyllene (**22**) (23.75%), bicyclogermacrene (**23**) (15.80%), and germacrene D (**24**) (11.73%) (Figure 9) [66, 67].

In 2016, a review published by Barros de Alencar and coworkers summarized many reports that identified the activity of diterpenes against NDs, including Chagas disease. The compounds and classes of compounds that were identified as most promising were abietic acid (**25**) derivatives, with IC_{50} values between $<20\ \mu\text{M}$ and $>150\ \mu\text{M}$ (Olmo et al., 2015); 12-hydroxy-11,14-diketo-6,8,12-abietatrien-19,20-olide (**26**) isolated from *Salvia cuspidate* with IC_{50} value of 5 $\mu\text{g/mL}$ (Lozano et al., 2015); 5-epi-icetexone (**27**) (10 mg/kg/day, i.p.) used for 5 days, capable of reversing infection in Swiss mice (Lozano et al., 2016); and aphidicolin (**28**) derivatives obtained by semisynthesis exhibited high potency and selectivity against parasitic amastigote forms (Santos et al., 2016). Two of these derivatives gave IC_{50} values of 0.6 μM (**28 A**) and 0.78 μM (**28 B**), with selectivity index >100 for both (Figure 10) [68, 69].

Other semisynthetic compounds were evaluated by Varela and colleagues. The EO obtained from the areal parts (leaves) of *Piper malacophyllum* (Piperaceae) presented two alkenylphenol derivatives as primary compounds: gibbilimbols A (**29**) and B (**30**), evaluated against promastigote/amastigote forms of *Leishmania infantum* and trypomastigote/amastigote forms of *T. cruzi*. Gibbilimbol B (**30**) showed better trypanocidal activity and lower toxicity to mammalian cells. These results encouraged researchers to prepare several quite simple synthetic analogues. Among these, the compound *n*-octyl-4-hydroxybenzylamine (LINS03003) (**31**) was the most potent, with IC_{50} values of 5.5 μM against amastigote forms of *T. cruzi*, with a higher activity than that of the natural prototype (Figure 11) [70].

Spurred on by the previous results, Varela's group isolated a new natural product from the *P. malacophyllum* EO — compound 5-[(3*E*)-oct-3-en-1-yl]-1,3-benzodioxole (**32**) (Figure 12), and a new set of five compounds were synthesized. The isolated compound was evaluated against *L. infantum* and *T. cruzi* and presented potential against promastigote/trypomastigote/amastigote forms of *T. cruzi*, with IC_{50} values of 32–83 μM and low toxicity ($CC_{50} > 200\ \mu\text{M}$ to mammalian cells). The synthetic compounds possessed promising antiparasitic activity; however, the compounds

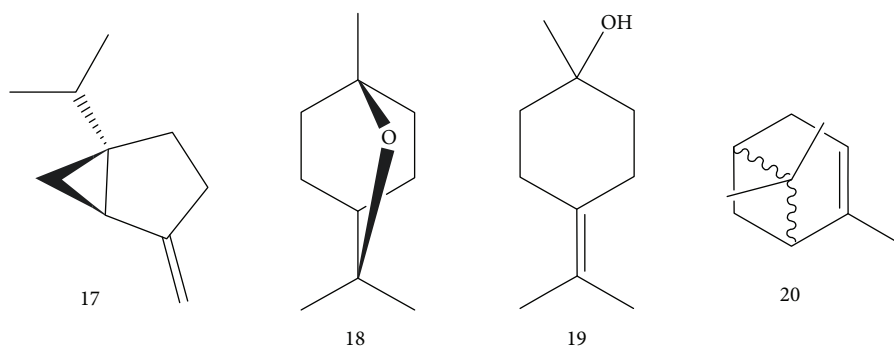


FIGURE 7: Chemical structure of the main constituent isolated from *Piper cubeba*.

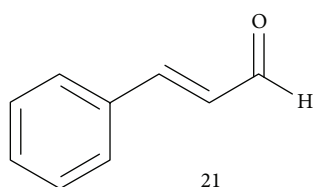


FIGURE 8: Chemical structure of (*E*)-cinnamaldehyde (**21**) - the main constituent identified in *Cinnamomum verum* EO.

were considered to be cytotoxic. Compound LINS03011 (**33**) (Figure 12) was the most active compound with IC_{50} values of 13.3 mM against amastigotes, comparable to the phenolic prototype LINS03003 (**31**), but with better selectivity index ($SI = 24.5$) and less toxicity [71].

Souza and coworkers evaluated the chemical composition and the *in vitro* effects of the EOs from the leaves of *Eugenia brejoensis* (*EbEO*), *Hyptis pectinata* (*HpEO*), *Hypenia salzmannii* (*HsEO*), *Lippia macrophylla* (*LmEO*), and seeds of *Syagrus coronata* (*ScEO*) against *T. cruzi*. GC-MS allowed the identification of 114 of 162 compounds. Among these, hydrocarbon sesquiterpenes were the most abundant found in *EbEO* (94.51%), *HfEO* (69.84%), *HpEO* (77.88%), and *HsEO* (56.16%). The *LmEO* fraction had monoterpenes as its principal constituents (98.08%). The EOs presented IC_{50} values between 29 and 110.6 mg/mL for epimastigote forms, 17.39–182.49 mg/mL for trypomastigote forms, and 12.5–408.33 mg/mL for amastigote forms of *T. cruzi*. The most active was *EbEO*, and the least active was *ScEO*. *EbEO* had as its main constituents δ -cadinene (**34**) (15.88%), *trans*-caryophyllene (**22**) (9.77%), and α -muurolol (**35**) (9.42%) (Figure 13) [72].

Villamizar et al. analyzed the trypanocidal effects of *Piper aduncum* EO (*PaEO*) and its main constituents against various forms of *T. cruzi*. GC-MS identified nerolidol and linalool (**3**) as the major *PaEO* components. *PaEO* showed $IC_{50}/24\text{ h} = 12.1\ \mu\text{g/mL}$ against metacyclic trypomastigotes and $IC_{50}/24\text{ h}$ values of $9\ \mu\text{g/mL}$ against amastigotes forms. Among the two main constituents isolated and identified, linalool (**3**) (Figure 2) was the best, showing trypanocidal activity with an $IC_{50}/24\text{ h}$ value of 306 ng/mL [73].

A recent study by Junior and colleagues evaluated the efficacy of the EO of *Syzygium aromaticum* (*SaEO*)

administered orally, alone, and in combination with benzimidazole (BZ) in mice infected with *T. cruzi* IV strain. GC-MS analysis identified eugenol (**2**) (82.2%) and γ -caryophyllene (**36**) (13.0%) (Figure 14) as the main components of *SaEO*. Treatment with *SaEO* promoted reduction in 1/5 parameters derived from the parasitemia curve when compared with untreated control groups. The groups treated with BZ and BZ + *SaEO* had reductions in 4/5 of these parameters, with similar profiles of the parasitemia curve. In addition, the animals treated with BZ and BZ + *SaEO* presented lower patency periods compared with animals treated only with *SaEO*, as well as lower positivity of blood cultures compared with the untreated control group. With respect to cure rates, *SaEO* showed 12.5% (1/8), BZ showed 25.0% (1/4), and BZ + *SaEO* showed 37.5% (3/8), considered a very interesting result [43].

1.2. Essential Oils and Components with Anti-*Trypanosoma brucei* Activity. *Trypanosoma brucei* (Trypanosomatid family) is the principal protozoan responsible for causing the type of trypanosomiasis known as sleeping sickness (or human African trypanosomiasis). It is classified as a neglected disease and is transmitted by tsetse flies (*Glossina* spp., Diptera: Glossinidae).

In humans, this infection is caused by two subspecies of *T. brucei* (*T. brucei gambiense*, predominant in the West Africa, and *T. brucei rhodesiense*, predominant in the East Africa). There is also *T. brucei brucei* that is infective only in animals. It is endemic to Sub-Saharan Africa. Despite the fact that it has been declining over the last two decades, *T. brucei* nevertheless affects approximately 30,000 people annually (as well as about 60 million people - distributed in 36 countries - that inhabit areas at risk), with high mortality rates, mainly in rural populations that have little access to necessary treatments, causing substantial socio-economic impact [74–86].

Human African trypanosomiasis, after parasite inoculations in the human host (or animal, *mutatis mutandis*), evolves in two stages. The primary stage is a hemolymphatic phase, or the parasitic cell replication stage, followed by a secondary meningoencephalitic phase, in which the parasites cross the blood-brain barrier and invade the central nervous system [86, 87]. This stage of the disease is characterized by a symptomatology including fever, headache, swelling of the lymph nodes, skin rashes, splenomegaly, confusion, sensory

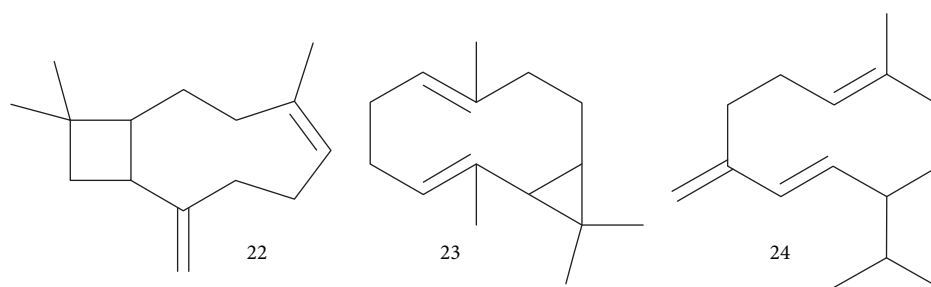


FIGURE 9: Chemical structure of (*E*)-caryophyllene (22), bicyclogermacrene (23), and germacrene (24) - main constituent identified in *Latana camara* EO.

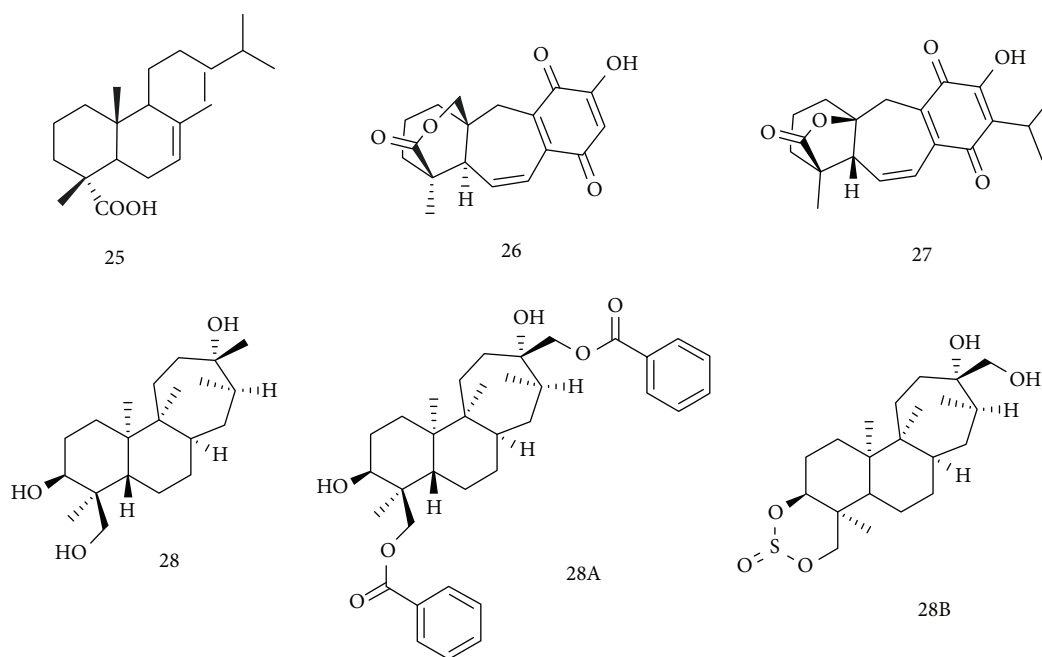


FIGURE 10: Chemical structure of abietic acid (25), 12-hydroxy-11,14-diketo-6,8,12-abietatrien-19,20-olide (26), 5-epi-icetexone (27), and aphidicolin (28) derivatives obtained by semisynthesis.

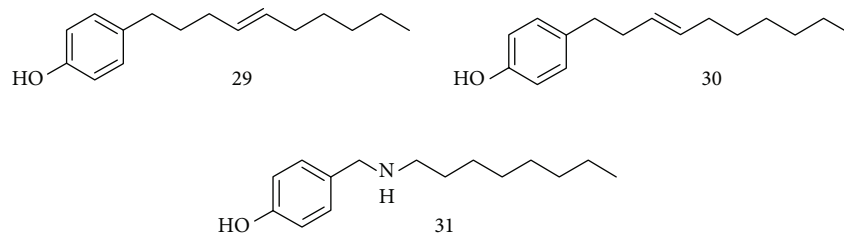


FIGURE 11: Chemical structure of alkenylphenol derivatives and its synthetic analogue (31).

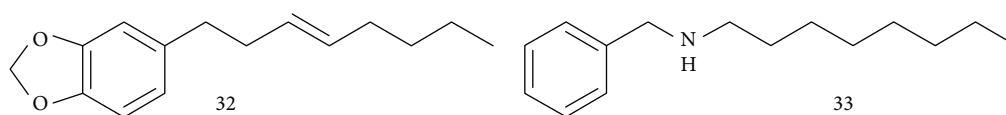


FIGURE 12: Chemical structures of 5-[(3*E*)-oct-3-en-1-yl]-1,3-benzodioxole (32) and LINS03011 (33).

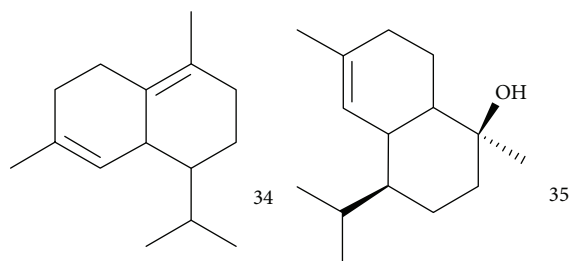


FIGURE 13: Chemical structure of the main constituents identified from *Eugenia brejoensis* EO.

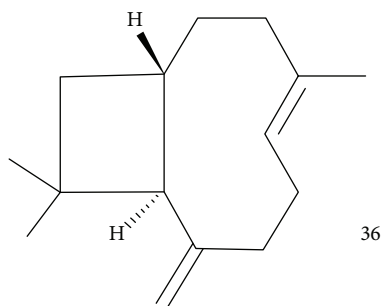


FIGURE 14: Chemical structure of γ -caryophyllene (36) - one of the main constituents identified from *Syzygium aromaticum* EO.

disturbances, motor coordination deficiency, and sleep disturbances (characteristic of the disease). It can be fatal if not properly treated [88].

The primary treatment is chemotherapy [89–91]; however, only four drugs are approved for human use: suramin, pentamidine, melarsoprol, and eflornithine [92]. The former two alternatives are used in the first stage of the disease, while the later two are used only in the last stage, representing alternatives of increased toxicity of the treatment [46, 88–92]. However, as was observed for the treatment of the other NDs, the treatment of *T. brucei* includes only a few effective drugs, and those that exist carry substantial toxicities, high costs, absence of sustainable production, and development of resistance by the protozoa [93–97]. There is an urgent need for the discovery and development of new drugs that are more efficient and secure. This need is reflected in the growing interest of many research groups in the search for new compounds with anti-*T. brucei* potential [98–106].

In many cases, traditional medicine has been the only alternative available for treatments based on natural plant products, and the treatment of *T. brucei* infections is no exception [64, 104, 107–114]. Natural plant products are excellent sources of safe and effective compounds to combat human African trypanosomiasis [88, 107, 115]. These natural bioactive products are for the most part plant secondary metabolites, including several classes of promising bioactive compounds, among which are EOs [92, 116–118].

As a reflection of the increasing interest in EOs for use against *T. brucei* evaluation, a number of investigators have studied their potential, from determination of vegetal sources

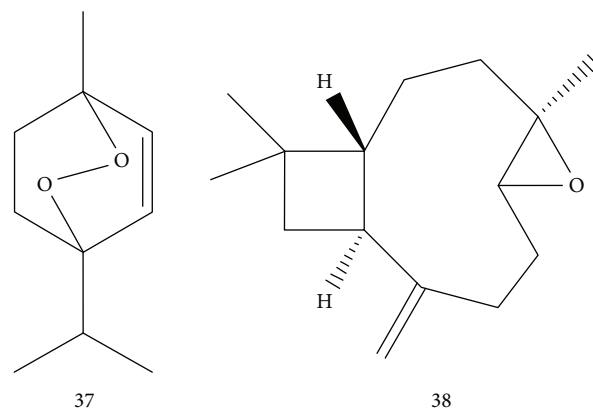


FIGURE 15: Chemical structures of ascaridole (37) and caryophyllene oxide (38) - one of the main components isolated from *C. ambrosioides* EO.

in various plant parts (aerial or radicular systems) to acquisition of species and types of essential oils.

In parallel with the increase in the use of EOs obtained from various parts of plants (aerial parts, fruits, flowers, and/or root systems) to combat sleeping sickness, several investigators worldwide have expanded their studies into the potential of these EOs and their main constituent chemicals against *T. brucei*.

One of these studies (Monzote and colleagues [64]) evaluated the EO from *Chenopodium ambrosioides* L. (CaEO), an aromatic plant with known biological potential from the Americas and Africa [119]. The plant's anti-*Leishmania* sp. activities have already been identified [120]. The main CaEO components carvacrol (10) (62%), ascaridole (37) (22%), and caryophyllene oxide (38) (5%) (Figure 15) demonstrated substantial growth inhibition of *T. brucei* parasites ($IC_{50} = 0.2 \pm 0.07 \mu\text{g/mL}$), with activity comparable to that of the standard drug suramin (IC_{50} of $0.05 \pm 0.05 \mu\text{g/mL}$). These results, demonstrating the broad antiprotozoal spectra of CaEO, are an example of the potential of their use in endemic areas where more than one infectious species is present.

EOs from *Cymbopogon* species have aroused interest of many research groups because of their antitrypanosomal activities, as the example of their growth inhibitory activity against *T. brucei* [121, 122]. Kpoviessi et al. [122] evaluated the EOs of fresh leaves from four *Cymbopogon* species consisting primarily of monoterpenes and sesquiterpenes (*C. citrates* - with 29 compounds, *C. giganteus* - with 53 compounds, *C. nardus* - with 28 compounds, and *C. schoenanthus* - with 41 compounds). The principal identified constituents were as follows: from *C. citrates*: geranial (6), neral (7), β -pinene (39), *cis*-geraniol (or nerol) (9), *cis*-verbenol (40), and geranyl acetate (41); from *C. giganteus*: *trans*-*p*-mentha-1(7),8-dien-2-ol (42), *trans*-carveol (43), *trans*-*p*-mentha-2,8-dienol (44), *cis*-*p*-mentha-2,8-dienol (45), *cis*-*p*-mentha-1(7),8-dien-2-ol (46), limonene (8), *cis*-carveol (47), *cis*-carvone (48), 4,4-dimethylandrost-5-en-3-one (49) and *trans*-carene-4,5-epoxy (50); from *C. nardus*: β -citronellol (51), elemol (52), limonene (8), α -cadinol (53), β -elemene

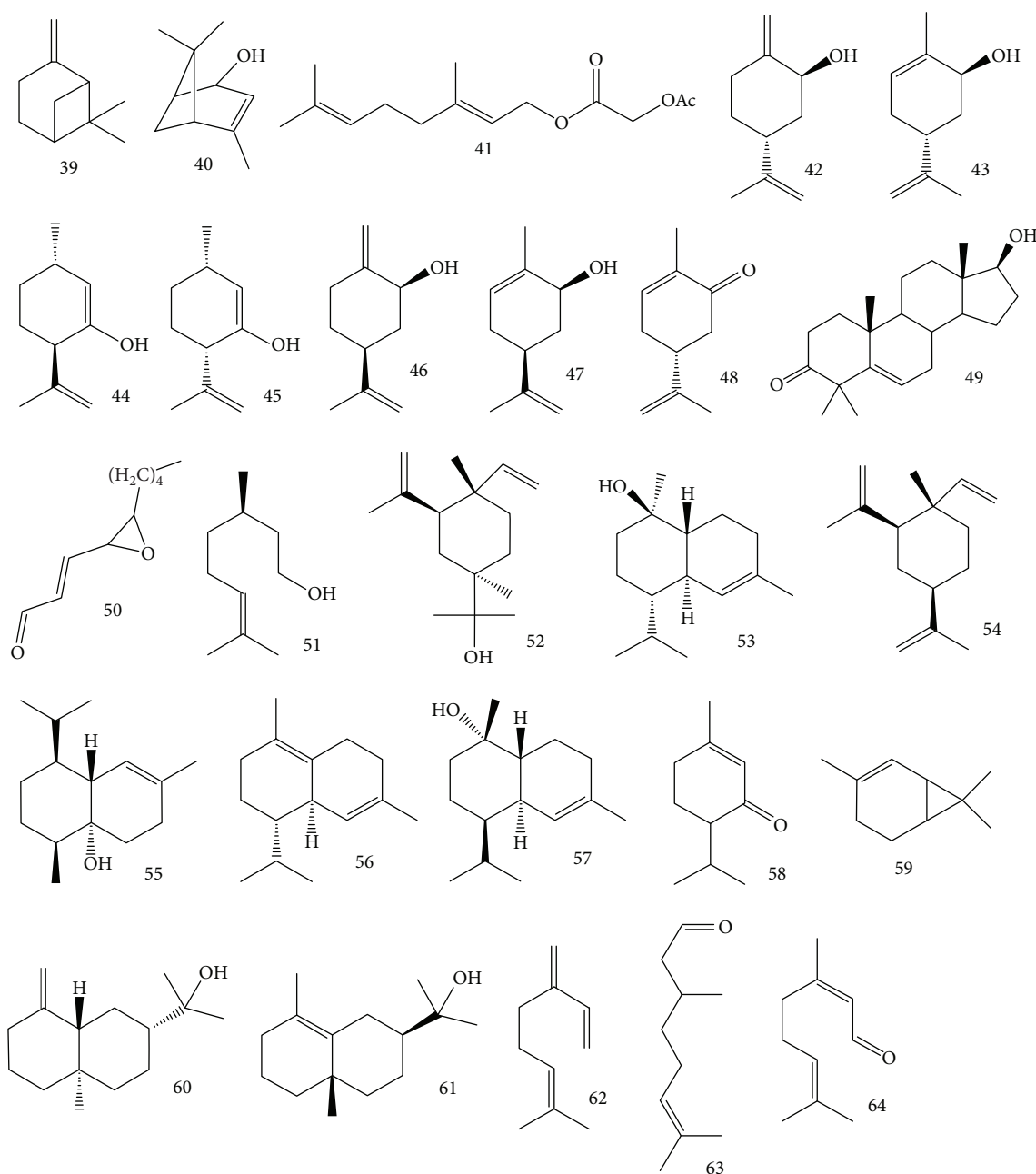


FIGURE 16: Chemical structures of several terpenes isolated from *Cymbopogon* species EO.

(54), cubenol (55), germacrene-D (24), geranyl acetate (41), δ -cadinene (34), and δ -cadinol (56); and from *C. schoenanthus*: piperitone (57), (+)-2-carene (58), limonene (8), elemol (52), β -eudesmol (59), *trans-p*-mentha-2,8-dienol (44), *cis-p*-mentha-2,8-dienol (45), and τ -eudesmol (60) (Figure 16).

These authors measured the cytotoxicity against WI38 and CHO cells and *in vitro* activity against *T. brucei*. All EOs evaluated were active, with IC_{50} values of $5.71 \pm 1.40 \mu\text{g/mL}$ for *C. nardus*, $2.10 \pm 0.89 \mu\text{g/mL}$ for *C. schoenanthus*, $1.83 \pm 0.13 \mu\text{g/mL}$ for *C. citrates*, and $0.25 \pm 0.11 \mu\text{g/mL}$ for *C. giganteus*. The reference drug suramin had an IC_{50} of $0.11 \pm 0.02 \mu\text{g/mL}$. *C. giganteus* EO was the most active oil

and demonstrated the largest selectivity index (SI of >200, as well as SI of 21.73 for *C. citrates*, 8.75 for *C. nardus*, and 23.81 for *C. schoenanthus*). The anti-*T. brucei* evaluation of some of the components from these EOs demonstrated high potentialities: β -myrcene (62) ($IC_{50} = 2.24 \mu\text{g/mL}$), citronellal (63) ($IC_{50} = 2.76 \mu\text{g/mL}$), *R*(+)-limonene (8) ($IC_{50} = 4.24 \mu\text{g/mL}$), citral (64) ($IC_{50} = 5.98 \mu\text{g/mL}$), and β -citronellol (51) ($IC_{50} = 6.45 \mu\text{g/mL}$) (Figure 16). Of these, limonene (8) was the principal component of three of the four EOs, including *C. giganteus* (the most active), probably tightly influencing their antitrypanosomal activities.

The composition of essential oils of *C. giganteus* was highly rich in oxygenated monoterpenes that should greatly

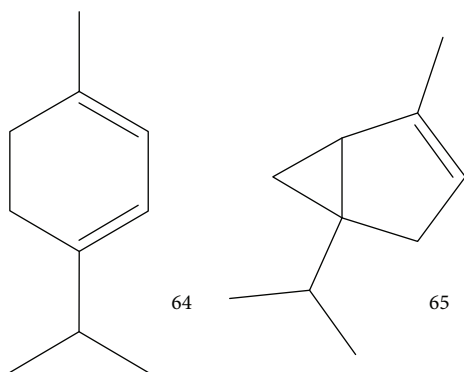


FIGURE 17: Chemical structures of γ -terpinene (**64**) and α -thujene (**65**) isolated from *Ocimum gratissimum*.

contribute their potential against *T. brucei*. The results showed that these compounds should be analyzed separately with greater depth in order to identify new alternatives for the treatment of human African trypanosomiasis.

Kpoviessi et al. [123] analyzed the EOs from the aerial parts (seeds, leaves, and stems) of *Ocimum gratissimum* in various vegetative stages. Their analysis of the principal EO components from *O. gratissimum* revealed 47 constituents (the majority of them hydrocarbons and a minority of oxygenated compounds). Of these, *p*-cymene (**11**), thymol (**1**), γ -terpinene (**64**), β -myrcene (**61**), and α -thujene (**65**) (Figure 17) were the most abundant. *O. gratissimum* EO demonstrated moderate anti-*T. brucei* activity (IC_{50} of $27.23 \pm 3.74 \mu\text{g/mL}$), as also previously observed with many of their principal compounds [94] as observed with thymol (**1**) (IC_{50} of $22.86 \mu\text{g/mL}$) and *p*-cymene (**11**) (IC_{50} of $76.32 \mu\text{g/mL}$). Thus, the primary isolated components did not possess strong anti-*T. brucei* activity and did not act synergistically (demonstrating an interesting selectivity index of 410 for the leaves and seeds portions). Conversely, the ethanolic extract of *O. gratissimum* demonstrated IC_{50} values less than $15 \mu\text{g/mL}$, leading us to believe that other bioactive compounds that were not present in the EO were responsible for the anti-*T. brucei* activity, justifying its continued use in traditional medicine.

Nibret and Wink [94] evaluated anti-*T. brucei* activity and cytotoxicity against human leukemic cells HL-60 in several plants with biological potentialities well-known in traditional Ethiopian medicine, including *Hagenia abyssinica* (female flower), *Leonotis ocymifolia* (aerial parts), and *Moringa stenopetala* (seeds). The results were compared to those of the standard drug diminazene aceturate ($IC_{50} = 0.088 \mu\text{g/mL}$ and $SI > 1464$). CG-MS revealed 20 components of *H. abyssinica* (including ledol (**66**), valerone (**67**), palustrol (**68**), *E*-15-heptadecenal (**69**), α -phellandren-8-ol (**70**), and verbenol (**40**) as primary compounds) and 68 components for *L. ocymifolia* (including caryophyllene oxide (**38**), palmitic acid (**71**), carotol (**72**), camphor (**14**), hexahydrofarnesyl acetone (**73**), estragole (**74**), and linalool (**3**) as the primary compounds) and for *M. stenopetala*, including benzyl isothiocyanate (**75**) and isobutyl isothiocyanate (**76**) as primary compounds. *M. stenopetala*

EO demonstrated greater antitrypanosomal activity (IC_{50} of $5.03 \mu\text{g/mL}$), but with a lower selectivity index ($SI = 2.31$). Among the isolated compounds, the best results were observed with benzyl isothiocyanate (**75**) ($IC_{50} = 1.20 \mu\text{g/mL}$ and $SI = 3.85$), cinnamaldehyde (**21**) ($IC_{50} = 2.93 \mu\text{g/mL}$ and $SI = 11.13$), styrene oxide (**78**) ($IC_{50} = 3.76 \mu\text{g/mL}$ and $SI = 19.92$), and ($-$)- α -cedrene (**79**) ($IC_{50} = 4.07 \mu\text{g/mL}$ and $SI = 5.45$). Cinnamaldehyde (**21**) and styrene oxide (**78**) (Figure 18) were the compounds with the best combined results (IC_{50} and SI). Nevertheless, they observed that benzyl isothiocyanate (**75**) was the majority component of *M. stenopetala* EO and was therefore responsible for the anti-*T. brucei* potentiality of this plant. Despite a low selectivity index, the compound can be utilized as a basis for developing new antitrypanosomal drugs.

Keetia leucantha, a plant used in traditional medicine of West African countries, was the object of study of Bero and colleagues [124]. They investigated the chemical composition of *KIOE* and their anti-*T. brucei* activities. The plant is used empirically in the treatment of sleeping sickness [102]. *K. leucantha* EO demonstrated IC_{50} values of $20.9 \pm 12.6 \mu\text{g/mL}$ for bloodstream forms of *T. brucei brucei* (compared to $IC_{50} = 0.11 \pm 0.02 \mu\text{g/mL}$ for the standard drug suramin). Analysis of the secondary metabolites contained in the OE returned 42 components, including *n*-hexadecanoic acid (43.46%) (**80**), oleic acid (9.51%) (**81**), phytol (5.68%) (**82**), tetradecanoic acid (**83**) (5.19%), and phytone (**84**) (4.3%) (Figure 19). Some of these compounds were also evaluated and presented moderate to weak activities, confirming the moderate activity of *KIOE* against *T. brucei*. The IC_{50} values of the isolated EO components were as follows: phytol (**82**) ($IC_{50} = 19.1 \pm 2.3 \mu\text{g/mL}$), oleic acid (**81**) ($IC_{50} = 64.3 \pm 0.5 \mu\text{g/mL}$), and *n*-hexadecanoic acid (**80**) ($IC_{50} > 100 \mu\text{g/mL}$). The best values were observed with the minority components: geranylacetone (**85**) ($IC_{50} = 16.2 \pm 12.5 \mu\text{g/mL}$), α -ionone (**86**) ($IC_{50} = 13.1 \pm 5.9 \mu\text{g/mL}$), and β -ionone (**87**) ($IC_{50} = 10.5 \pm 5.8 \mu\text{g/mL}$) (Figure 19). These components were evaluated against procyclic forms of *T. brucei*, and they were found to be even less active. According to the authors, these results can be an indication of the mechanisms of action of inhibition of *T. brucei brucei* growth. The authors suggest inhibition of glycolysis as a possible mechanism of action, as this is the main pathway of ATP synthesis for the bloodstream forms that do not possess the Krebs cycle or mitochondrial respiratory chain coupled to ATP. This phenomenon may explain their greater sensitivities compared with procyclic forms, highlighting the inhibitory activity of β -ionone (**87**) against glyceraldehyde-3-phosphate dehydrogenase ($32.6\% \pm 3.4\%$ at $20 \mu\text{g/mL}$); however, the inhibitory effect was not significant for α -ionone (**86**) ($0.00\% \pm 7.2\%$ at $20 \mu\text{g/mL}$) or phytol (**82**) ($6.8\% \pm 0.7\%$ at $20 \mu\text{g/mL}$).

Another well-known plant in traditional medicine, *Mentha crispa*, was evaluated for EO activity by Sousa et al. [125]. They studied four activities against *T. brucei* bloodstream forms, as well as their cytotoxicity against human leukemic cells (HL-60). Phytochemical analysis identified major EO components, including rotundifolone (**88**) (58.11%),

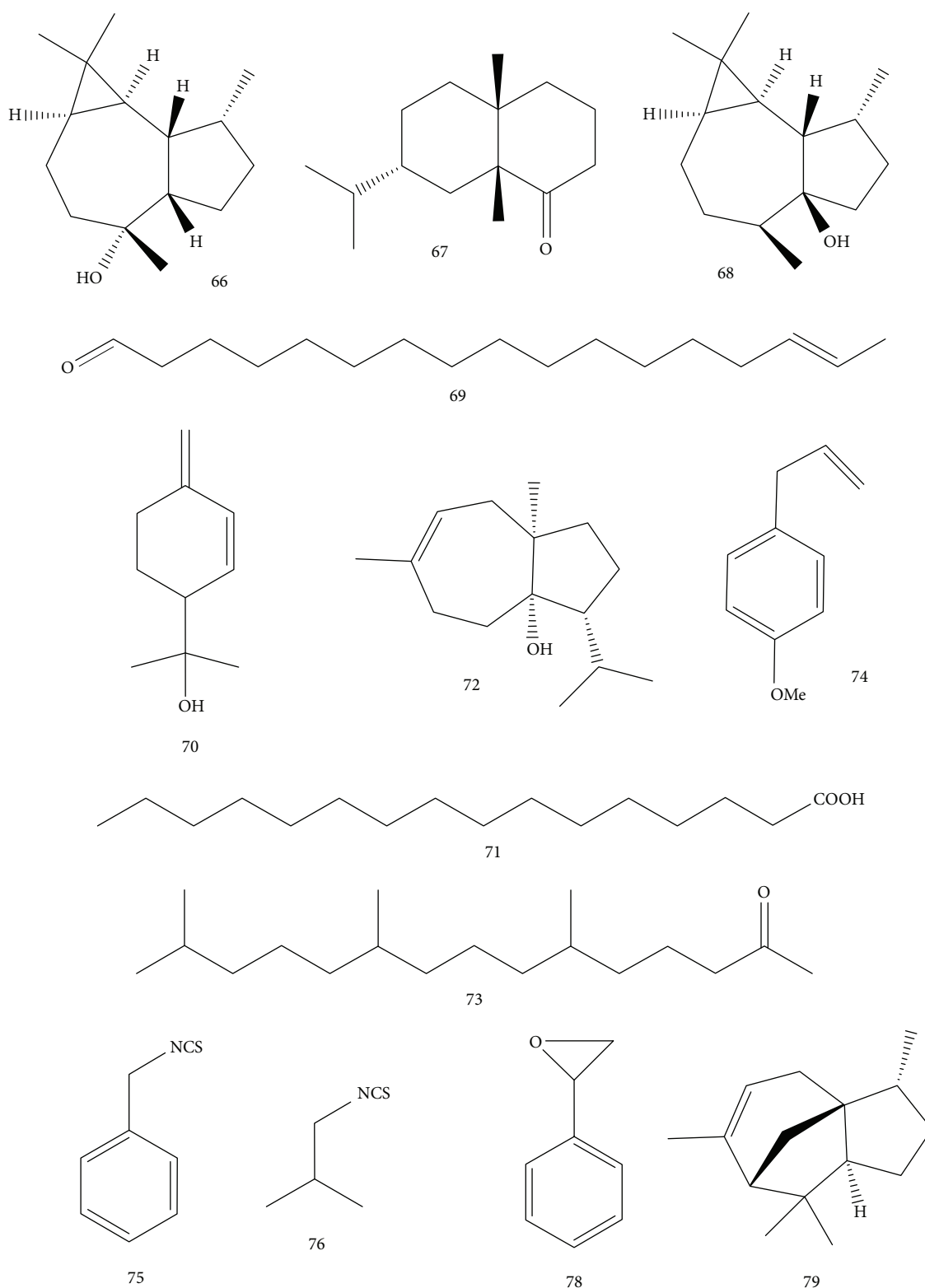


FIGURE 18: Chemical structures of constituents isolated from plants used in traditional Ethiopian medicine.

limonene (**8**) (10.58%), myrcene (**61**) (7.79%), germacrene (**24**) (6.55%), *cis*- β -ocimene (**89**) (5.01%), and β -pinene (**39**) (4.43%), as well as four other monoterpenic analogues: (+)-limonene epoxide (**90**), (-)-limonene epoxide (**90**), (-)-perillyl alcohol (**91**), and (-)-perillyl aldehyde (**92**)

(Figure 20). The isolated compounds and the EO demonstrated dose-dependent activity in their minimum inhibitory concentration (MIC) values, varying from 1 to 100 μ /mL, and their GI_{50} , varying from 0.3 to 13.3 μ g/mL, compared to the standard drug suramin (MIC = 0.1 μ g/mL, GI_{50} = 0.05 \pm

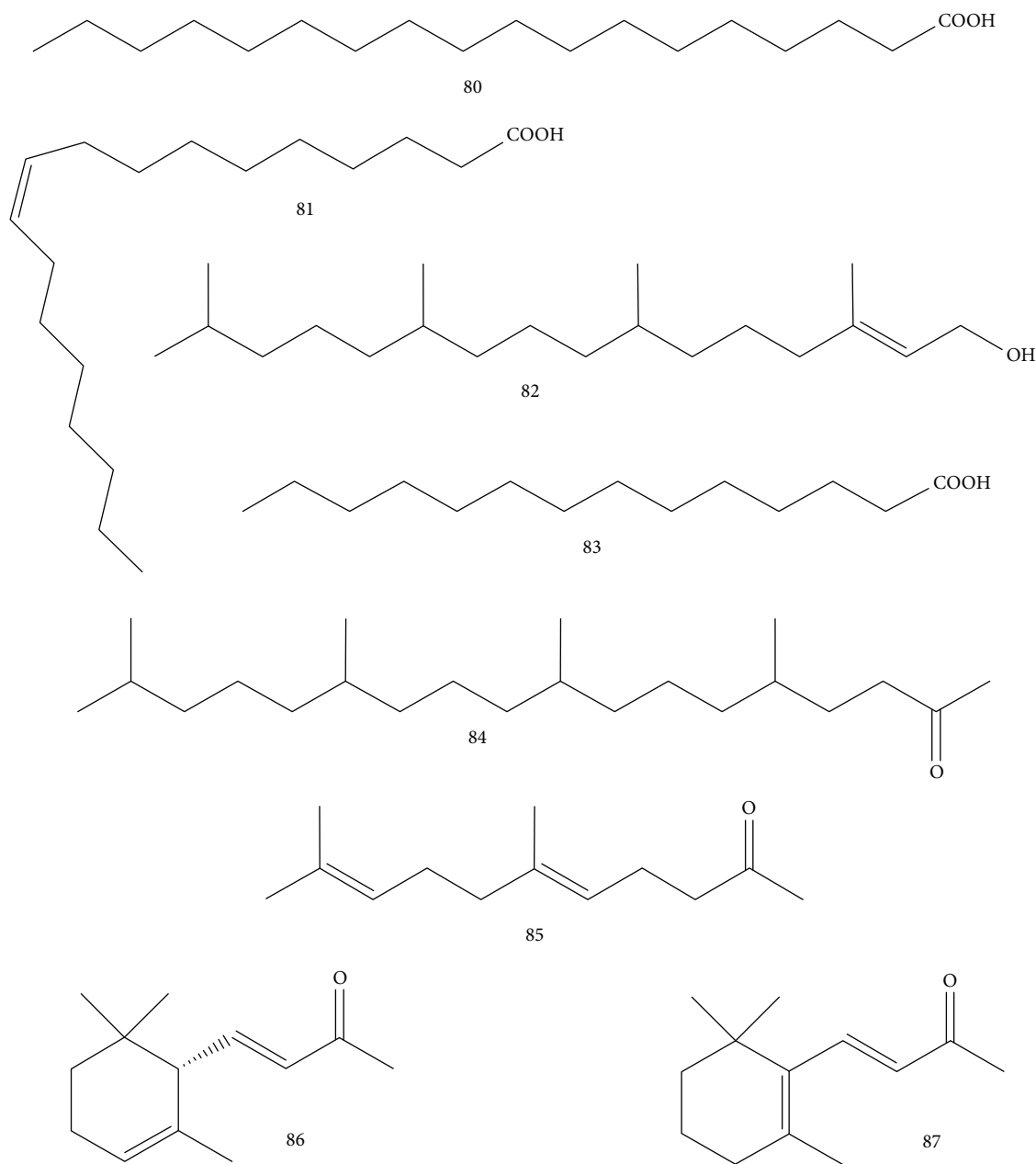


FIGURE 19: Chemical structures of some compounds isolated from *Keetia leucantha*.

0.003 $\mu\text{g}/\text{mL}$, $\text{SI} \geq 2000$). Greater potentialities were observed for *McEO* ($\text{MIC} = 1 \mu\text{g}/\text{mL}$, $\text{GI}_{50} = 0.33 \pm 0.03 \mu\text{g}/\text{mL}$, $\text{SI} = 25$), rotundifolone (**88**) ($\text{MIC} = 1 \mu\text{g}/\text{mL}$, $\text{GI}_{50} = 0.32 \pm 0.05 \mu\text{g}/\text{mL}$, $\text{SI} = 10.6$), and (-)-perillyl aldehyde (**92**) (Figure 20) ($\text{MIC} = 1 \mu\text{g}/\text{mL}$, $\text{GI}_{50} = 0.31 \pm 0.02 \mu\text{g}/\text{mL}$, $\text{SI} = 45$). These compounds were only slightly less active than the reference drug. The presence of rotundifolone (**88**) as the major component in the *McEO* should be the primary compound responsible for its high anti-*T. brucei* activity.

Structurally comparing these major components with other analogues, the presence of an α,β -unsaturated carbonyl appeared to favor anti-*T. brucei* activity, because when these components were absent there was significant loss of activity. The change in the position of this α,β -unsaturated carbonyl,

and the change of position of an additional unsaturation outside of the ring, appeared to strongly influence the cytotoxicity in HL-60, where (-)-perillyl aldehyde (**92**) showed less toxicity than did rotundifolone (**88**), but with a better selectivity index [125].

Habila et al. [115] investigated the potential activity against *T. brucei brucei* of EOs from four plants (*Cymbopogon citratus* – leaves, *Eucalyptus citriodora* – leaves, *Eucalyptus camaldulensis* – leaves, and *Citrus sinensis* – fruit peels). CG-MS of EOs demonstrated an abundance of cyclobutane (**93**) (96.08%) in *C. sinensis*; eucalyptol (**18**) (75.04%), bicyclo[3.1.1]hept-2-ene (**94**) (10.27%), benzene (**95**) (6.23%), and cyclohexene (**96**) (4.92%) in *E. camaldulensis*; 6-octenal (**97**) (77.11%) and 6-octen-1-ol (**98**) (14.09%) in *E.*

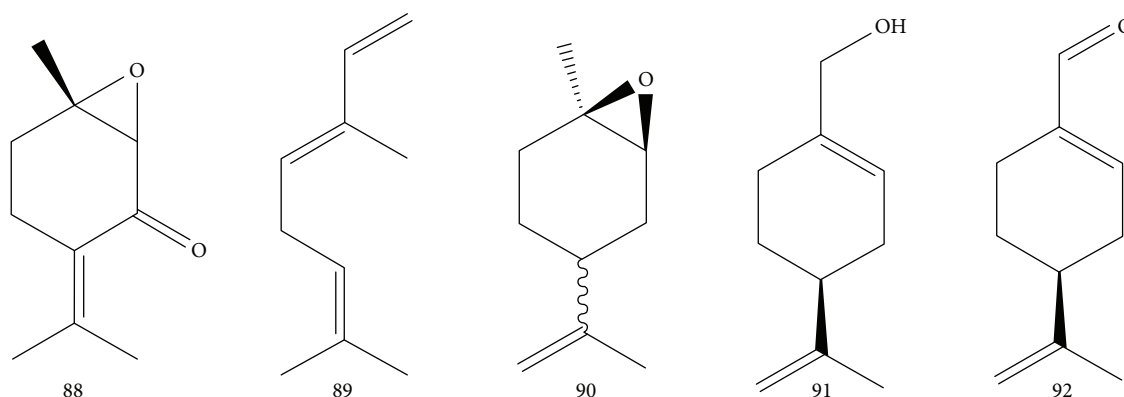


FIGURE 20: Chemical structures of rotundifolone (**88**), (-)-perillyl aldehyde (**92**), and other compounds isolated from *Mentha crisper* EO.

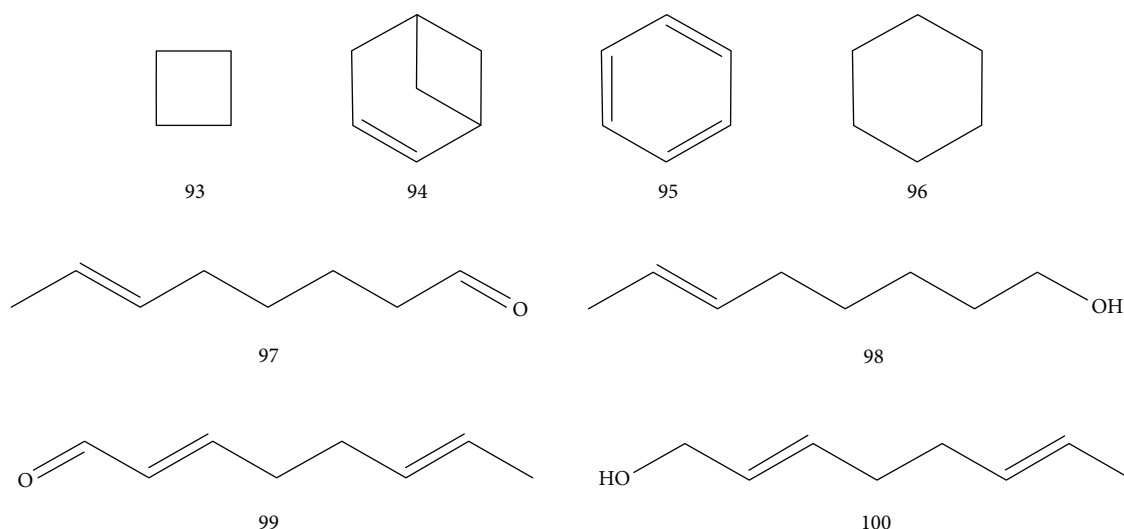


FIGURE 21: Chemical structures of main constituents isolated from *Cymbopogon citratus* – leaves, *Eucalyptus citriodora* – leaves, *Eucalyptus camaldulensis* – leaves, and *Citrus sinensis* – fruit peels.

citriodora; and citral (**63**) (38.32%) and 2,6-octadienal (**99**) (35.05%) and 2,6-octadien-1-ol (**100**) (26.63%) in *C. citratus* (Figure 21).

The death of the parasites was observed after the use of 0.4 g/mL of the EOs. The EO most capable of killing parasites quickly was the *C. citratus* EO (3 min). EOs from *E. citriodora* and *E. camaldulensis* killed parasites in 4 minutes, and *C. sinensis* EO killed parasites in 5 min. In smaller doses, the time of death increased to 6 min (0.2 g/mL) and 15 min (0.1 g/mL) for *C. sinensis*, 8 min (0.2 g/mL) and 17 min (0.1 g/mL) for *E. camaldulensis*, 8 min (0.2 g/mL) and 22 min (0.1 g/mL) for *E. citriodora*, and 4 min (0.2 g/mL) and 11 min (0.1 g/mL) for *C. citratus*. Thus, their activities appeared to be dose-dependent and the four EOs demonstrated powerful activity, causing the death of protozoa in short periods of time, compared with that of the reference drug (diminaveto) that promoted the death of the parasites in equivalent times.

Gutiérrez et al. [126] evaluated a species of the *Piper* genus, a well-known source of bioactive compounds [127].

Piper ossanum (leaves) was collected in two locations in Cuba (Bauta and Ceiba). Chromatograms of the EOs demonstrated the presence of 43 components for the Bauta species (*PoB*) and 39 for the Ceiba species (*PoC*). In both, the primary components were piperitone (**57**), camphene (**15**), camphor (**14**), and viridiflorol (**101**) (Figure 22), with *PoB* being more abundant (20.07% for *PoB*, and 19.01% for *PoC*). Some quantitative differences were observed in *PoB* and *PoC* EO constituents: camphor (**14**) (13.87% for *PoB* and 9.41% for *PoC*), viridiflorol (**101**) (12.97% for *PoB* and 18.80% for *PoC*), and camphene (**15**) (7.41% for *PoB* and 5.39% for *PoC*). *PoB* has as minor components *p*-cymene (**11**), sylvestrene (**102**), (*Z*)- and (*E*)- β -ocimene (**89**), terpinen-4-ol (**103**), cubebol (**104**), and humulene epoxide (**105**); *PoC* possessed small quantities of β -phellandrene (**106**), γ -muurolene (**107**), spathulenol (**108**), and globulol (**109**) (Figure 22). The values of the sensitivity of *T. brucei* against the EOs showed no significant difference in terms of IC_{50} values (8.1 μ g/mL for *PoB* and 8.4 μ g/mL for *PoC*), suggesting that the various compositions of their constituents were not

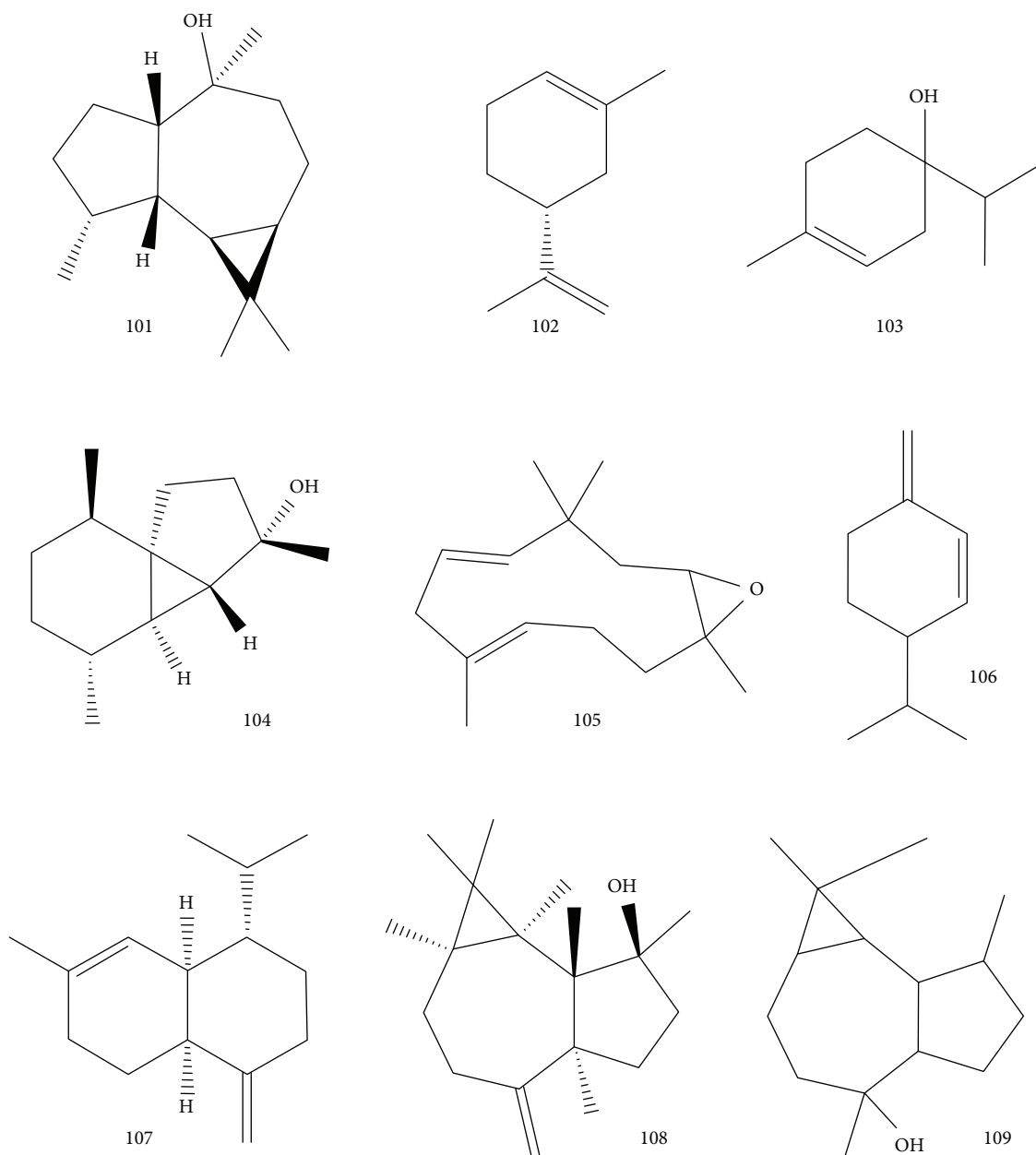


FIGURE 22: Chemical structures of isolated terpenoids from *Piper* genus.

decisive for a differentiation of their potential, classified as weak when compared to the standard drug suramin ($IC_{50} = 0.05 \mu\text{g/mL}$). Both EOs demonstrated low toxicity in a human fetal lung fibroblast cell line (MRC-5) ($4.2 \mu\text{g/mL}$ for PoB and $0.95 \mu\text{g/mL}$ for PoC). Evaluation of the *T. brucei* activity of the main compounds of each EO is necessary in order to identify more promising compounds.

Strychnos spinosa leaves are widely utilized in African trypanosomiasis treatment [128]. Hoet et al. [129] studied the cytotoxicity and the anti-*T. brucei brucei* activity of SsEO leaves and 16 of their components. SsEO leaves contained more than 100 constituents, including palmitic acid (**71**) (34.3%), linalool (**3**) (16%), (*E*)-phytol (**82**) (6.7%), and (*E*)-geraniol (**6**) (4%). SsEO showed moderately activity

($IC_{50} = 13.5 \mu\text{g/mL}$) and weak selectivity index ($SI = 4.4$). Of the pure components tested, the prominent compounds were (*E*)-nerolidol (**110**) (Figure 23) ($IC_{50} = 1.7 \pm 0.05 \mu\text{g/mL}$, $SI = 35.7$), linalool (**3**) ($IC_{50} = 2.5 \pm 0.3 \mu\text{g/mL}$, $SI \geq 40$), (*E*)-geranylacetone (**85**) ($IC_{50} = 5.2 \pm 0.6 \mu\text{g/mL}$, $SI \geq 19.2$), β -ionone (**87**) ($IC_{50} = 5.5 \pm 0.2 \mu\text{g/mL}$, $SI = 11.7$), (*E*)-phytol (**82**) ($IC_{50} = 6.2 \pm 0.2 \mu\text{g/mL}$, $SI = 3.4$), and α -terpineol (**111**) (Figure 23) ($IC_{50} = 7.0 \pm 3.3 \mu\text{g/mL}$, $SI \geq 14.3$). Among these, only linalool (**3**) and (*E*)-phytol (**82**) were found in abundance in SsEO, leading to the conclusion that interaction with other compounds decreased the activity of the EO. In addition, the presence in minimal quantities of the more active compounds (identified as minority components) prevented the EOs from exerting their potential effects. Palmitic

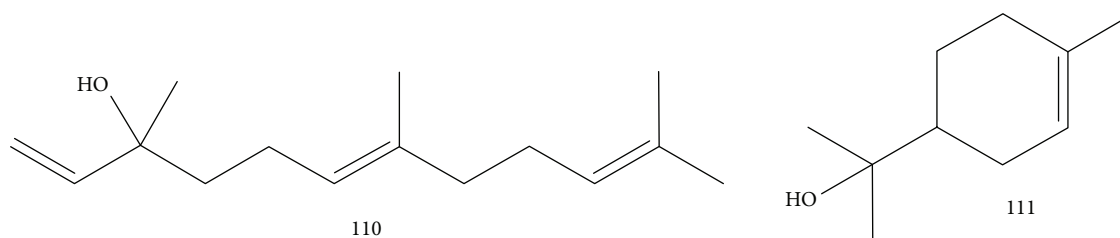


FIGURE 23: Chemical structure of (*E*)-nerolidol (**110**) and α-terpineol (**111**) – active compounds with anti-*T. brucei brucei* activity, isolated from *Strychnos spinosa* EO.

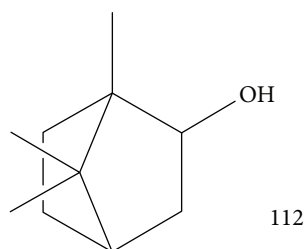


FIGURE 24: Chemical structure of borneol (**112**) – one of the compounds identified in the *Kadsura longipedunculata* EO.

acid (**71**), the primary component for this species, was inactive and highly toxic (SI = 0.6).

Preliminary results [101] demonstrated good antitrypanosomal activity of dichloromethane extracts of *S. spinosa* ($IC_{50} = 1.5 \mu\text{g/mL}$), causing us to speculate that there are active components that are not EO constituents that should be evaluated more intensively. The better results observed with linalool (**3**) and (*E*)-nerolidol (**110**) reflect the need for further studies of these substances and for investigation of the potential of other oxygenated terpenes to identify alternatives for human African trypanosomiasis treatment.

Mulyaningsih et al. [130] investigated the *Kadsura longipedunculata* EO that had 50 identified components. The EO fraction was composed of 75% sesquiterpenes and 22.63% monoterpenes, including δ-cadinene (**34**) (21.79%), camphene (**15**) (7.27%), borneol (**112**) (6.05%) (Figure 24), cubenol (**55**) (5.12%), and δ-cadinol (**56**) (5.11%). *KIEO* and camphene (**15**) were evaluated against bloodstream forms of *T. brucei brucei* and human hepatocellular liver carcinoma (HepG2); however, the results were not encouraging. *KIEO* had an IC_{50} of $50.52 \pm 0.029 \mu\text{g/mL}$ and an IC_{50} of $136.96 \mu\text{g/mL}$. The IC_{50} of the pure compounds were $80.66 \pm 0.87 \mu\text{g/mL}$ for camphene (**15**) and $70.00 \pm 1.28 \mu\text{g/mL}$ for borneol (**112**), both unfavorable cytotoxicity profiles. These results indicate that the active substances of *K. longipedunculata* useful against human African trypanosomiasis treatment were not part of their EO constituents.

Hamdan and coworkers [131] evaluated the EOs of two Egyptian species of *Citrus* sp., *C. jambhiri* and *C. pyriformis*. For both species, 94 compounds were identified, with limonene (**8**) the major compound (92.48% for *C. jambhiri* and 75.56% for *C. pyriformis*). Both EOs had poor activity against bloodstream forms of *T. b. brucei*, with IC_{50} values of $72.47\% \pm 0.87 \mu\text{g/mL}$ for *C. jambhiri*

and of $71.29 \pm 0.38 \mu\text{g/mL}$ for *C. pyriformis*, much less active than the standard drug diminazene aceturate ($IC_{50} = 0.0832 \pm 0.0003 \mu\text{g/mL}$).

Cruz et al. [119] evaluated the *Eugenia uniflora* EO from leaves and identified 87 compounds (spathulenol (**108**) – 15.8%, α-copaene (**113**) – 10.96%, muurola-4,10-dien-1β-ol (**114**) – 9.3%, caryophyllene oxide (**38**) – 8.93%, allo-aromadendrene (**115**) – 5.5%, and nootkatone (**116**) – 5.17%) (Figure 25). The oxygenated sesquiterpenes (54.09%) were the most abundant class of compounds. An *in vitro T. b. brucei* evaluation demonstrated moderate activity of *EuEO* ($IC_{50} = 11.20 \pm 2.17 \mu\text{g/mL}$) with a weak selectivity index (SI = 6.82). The reference drug suramin had an IC_{50} of $0.16 \pm 0.03 \mu\text{g/mL}$.

Petrelli et al. [132] investigated the EO of *Erigeron floribundus* aerial parts, containing 85 constituents. The primary class of constituents was sesquiterpenes (60.4% – being 38.5% oxygenated and 21.9% hydrocarbons). The main components were caryophyllene oxide (**38**) (12.4%), spathulenol (**108**) (12.2%), (*E*)-β-farnesene (**117**) (Figure 26) (5.5%), and (*E*)-caryophyllene (**22**) (4.2%), in addition to limonene (**8**) (8.8%). *EfEO* was evaluated for its antitrypanosomal activity against *T. brucei* and cytotoxicity in a human breast adenocarcinoma cell line (A375). There was moderate activity ($IC_{50} = 33.5 \pm 2.7 \mu\text{g/mL}$) with a low selectivity index value (SI ≥ 5.97). Their main constituent, caryophyllene oxide (**38**), was also assayed and showed up inactive, reflecting the low antitrypanosomal activity of the EO. However, the evaluation of another potential major component, limonene (**8**), demonstrated promising activity ($IC_{50} = 5.6 \pm 1.6 \mu\text{g/mL}$ and SI ≥ 17.85), being the main contributor to the expression of EO potentiality. The authors concluded that this difference of activity in favor of limonene (**8**) could be attributed to the degree of its unsaturation, in addition to its exocyclic methylene group. The occurrence of a possible binding site with SH groups of proteins may be an indicator of their mechanism of action. However, this speculation requires more detailed investigation.

EOs from aerial parts of a variety of plant species were analyzed by Costa et al. [88], including *Cymbopogon citratus* L. (leaves), *Distichoselinum tenuifolium* (aerial parts), *Juniperus oxycedrus* (leaves and berries), *Lavandula luisieri* (influorescences), *Lavandula viridis* (aerial parts), *Lippia graveolens* (aerial parts), *Mentha cervina* (leaves), *Mentha x piperita* (leaves), *Origanum virens* (leaves), *Rosmarinus officinalis* (leaves), *Seseli tortuosum* (aerial parts), *Syzygium aromaticum* (floral buttons), *Thymbra capitata* (aerial parts),

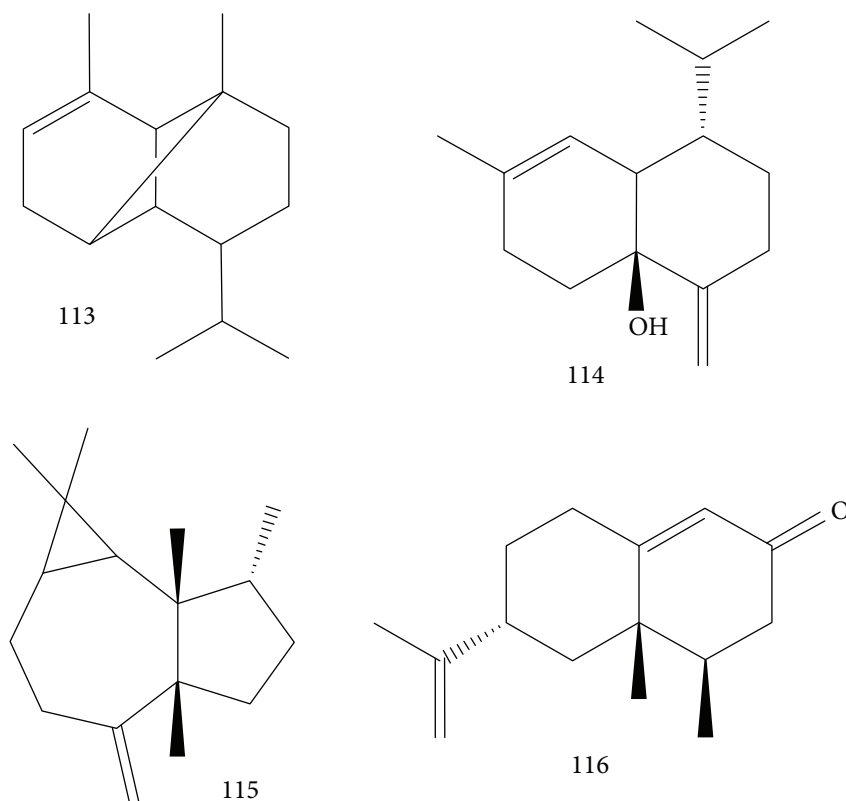


FIGURE 25: Chemical structure of compounds isolated from *Eugenia uniflora* EO.

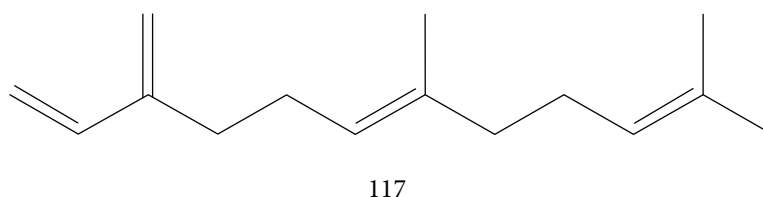


FIGURE 26: Chemical structure of (*E*)- β -farnesene (117) – one constituent from *Erigeron floribundus* EO.

Thymus capitellatus (aerial parts), *Thymus mastichina* (leaves), and *Thymus zygis sylvestris* (leaves).

CG-MS allowed identification of the main components, including geranial (**6**) (45.7%), neral (**7**) (32.5%), and β -myrcene (**61**) (11.5%) for *C. citratus*; β -myrcene (**61**) (84.6%) and limonene (**8**) (2.2%) for *D. tenuifolium*; α -pinene (**118**) (54.7%), germacrene D (**24**) (10.4%), and β -myrcene (**61**) (17.8%) for the berries of *J. oxycedrus*; α -pinene (**118**) (65.5%), Δ -3-carene (**119**) (5.7%), β -phellandrene (**106**) (3.2%), and β -myrcene (**61**) (2.7%) for leaves of *J. oxycedrus*; 1,1,2,3-tetramethyl-4-hydroxymethyl-2-cyclopentene (**120**) (2.4%), 2,3,4,4-tetramethyl-5-methylene-cyclopent-2-enone (**121**) (5.2%), trans- α -necrotyl acetate (**122**) (16.0%), lyratyl acetate (**123**) (3.5%), 1,8-cineole (**124**) (18.9%), lavandulyl acetate (**125**) (7.2%), linalool (**3**) (3.1%), and α -pinene (**118**) (2.3%) for *L. luisieri*; 1,8-cineole (**124**) (29.7%), camphor (**14**) (10.0%), α -pinene (**118**) (9.2%), linalool (**3**) (9.0%), selina-3,7(11)-diene (**126**) (6.6%), *Z*- α -bisabolene

(**127**) (6.3%), borneol (**112**) (2.7%), and camphene (**15**) (2.7%) for *L. viridis*; thymol (**1**) (19.8%), *p*-cymene (**11**) (16.9%), 1,8-cineole (**124**) (6.6%), caryophyllene oxide (**38**) (5.7%), linalool (**3**) (5.4%), Δ -3-carene (**119**) (4.3%), α -terpineol (**111**) (3.6%), myrcene (**61**) (3.4%), *E*-caryophyllene (**22**) (2.4%), and trans-sabinene hydrate (**17**) (2.3%) for *L. graveolens*; pulegone (**128**) (74.8%), isomenthone (**129**) (10.6%), and limonene (**8**) (5.4%) for *M. cervina*; menthol (**130**) (44.0%), menthofuran (**131**) (10.9%), menthone (**132**) (9.8%), menthyl acetate (**133**) (7.8%), 1,8-cineole (**124**) (5.8%), neo-menthol (**134**) (4.0%), neo-isomenthol (**135**) (2.9%), and pulegone (**128**) (2.4%) for *M. x piperita*; carvacrol (**10**) (68.2%), γ -terpinene (**64**) (7.9%), *p*-cymene (**11**) (7.4%), β -myrcene (**61**) (2.4%), and thymol (**1**) (2.1%) for *O. virens*; β -myrcene (**61**) (32.0%), 1,8-cineole (**124**) (13.7%), camphor (**14**) (11.9%), α -pinene (**118**) (11.1%), limonene (**8**) (6.6%), *p*-cymene (**11**) (3.8%), camphene (**15**) (3.4%), and linalool (**3**) (2.1%) for *R. o. cinalis*; α -pinene

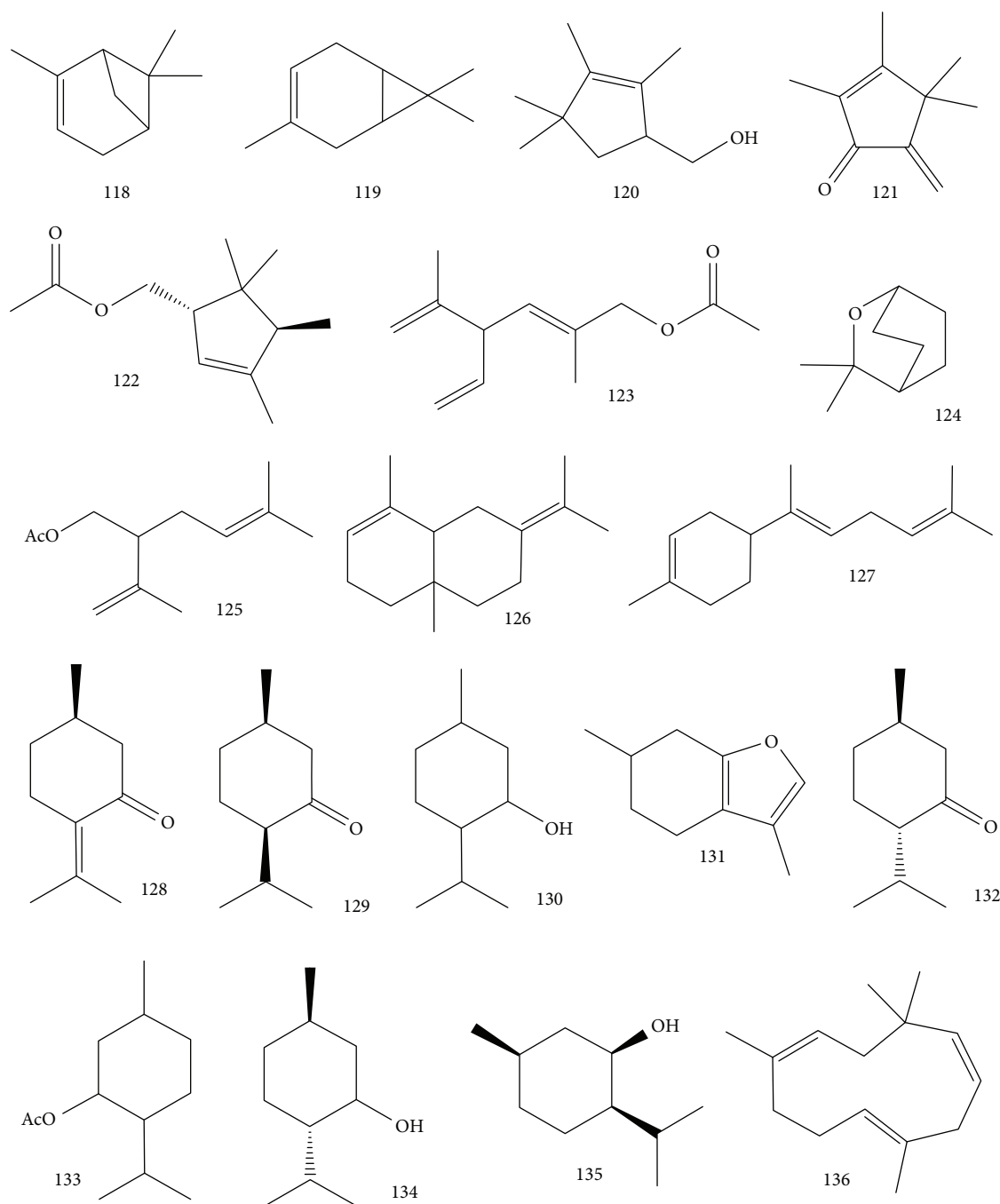


FIGURE 27: Chemical structure of main components identified in the study of Costa et al. [88].

(**118**) (27.4%), β -pinene (**39**) (16.0%), limonene (**8**) (10.0%), γ -terpinene (**64**) (9.3%), (*Z*)- β -ocimene (**89**) (8.0%), β -myrcene (**61**) (3.0%), camphene (**15**) (2.1%), and sabinene (**17**) (2.0%) for *S. tortuosum*; eugenol (**2**) (85.3%) and humulene (**136**) (6.8%) for *S. aromaticum*; carvacrol (**10**) (74.6%), *p*-cymene (**11**) (5.5%), *E*-caryophyllene (**22**) (3.9%), γ -terpinene (**64**) (3.6%), and linalool (**3**) (2.8%) for *T. capitata*; 1,8-cineole (**124**) (58.6%), borneol (**112**) (10.0%), camphene (**15**) (6.5%), α -pinene (**118**) (4.5%), sabinene (**17**) (3.0%), and β -pinene (**39**) (2.0%) for *T. capitellatus*; 1,8-cineole (**124**) (67.4%), linalool (**3**) (4.3%), β -pinene (**39**) (4.0%),

α -terpineol (**111**) (3.5%), α -pinene (**118**) (3.0%), and sabinene (**17**) (2.4%) for *T. mastichina*; and geranyl acetate (**41**) (44.5%), geraniol (**6**) (33.1%), and camphor (**14**) (3.9%) for *T. zygis sylvestris* (Figure 27).

Of all these EOs, noteworthy findings were as follows: JoEO berries ($IC_{50} = 0.9 \mu\text{g/mL}$ and $SI = 63.4$), CcEO ($IC_{50} = 3.2 \mu\text{g/mL}$ and $SI = 9.0$), and LfEO ($IC_{50} = 5.7 \mu\text{g/mL}$ and $SI = 11.9$). Some pure compounds were also evaluated, and the best IC_{50} values were obtained with α -pinene (**118**) ($IC_{50} = 2.9 \mu\text{g/mL}$) and citral (**63**) ($IC_{50} = 18.9 \mu\text{g/mL}$). α -Pinene (**118**) is the main component of the most active

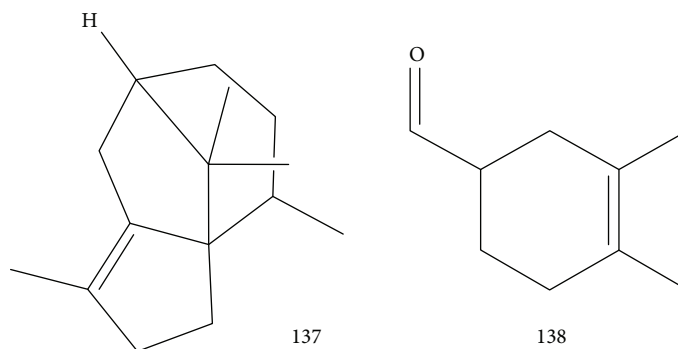


FIGURE 28: Chemical structure of cyperene (**137**) and 3,4-dimethylcyclohex-3-ene-1-carbaldehyde (**138**) – some main components identified from *Aframomum sceptrum* EO.

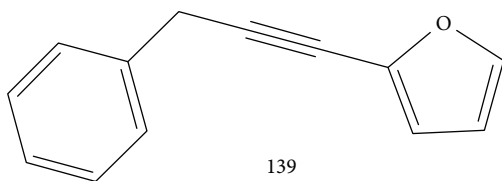


FIGURE 29: Chemical structure of carlina oxide (**139**) – main component of *Carlina acaulis* root EO.

EO (*Juniperus oxycedrus*), contributing to its high anti-*T. brucei* activity. Because the same result was not observed with JoEO leaves, the authors speculated that the synergistic effects on the most promising species potentiated their effects, suggesting that their interactions with germacrene D (**24**) and β -myrcene (**61**) should be further investigated [88].

Cheikh-Ali et al. [133] evaluated the EO from *Aframomum sceptrum* rhizomes. AsEO consists of 75 compounds, including β -pinene (**39**) (12.71%), caryophyllene oxide (**38**) (10.03%), cyperene (**137**) (5.99%), 3,4-dimethylcyclohex-3-ene-1-carbaldehyde (**138**) (3.40%), α -pinene (**118**) (2.78%), β -caryophyllene (**22**) (2.33%), α -terpineol (**111**) (2.12%), *D*-limonene (**8**) (1.89%), 1,8-cineole (**124**) (1.84%), and α -caryophyllene (or humulene) (**136**) (1.1%) (Figure 28). The minimum lethal concentration (MLC) against *T. brucei brucei* was determined for the EO (MLC = 1.47 mg/mL) and for some pure compounds, β -pinene (**39**) (MLC > 0.1 mg/mL) and caryophyllene oxide (**38**) (MLC = 0.1 mg/mL). When compared to the reference drug pentamidine (MLC = 7.4 μ g/mL), this EO and their components showed very good anti-*T. brucei* activities.

Herrmann et al. [134] obtained the *Carlina acaulis* root EO and identified carlina oxide (**139**) (Figure 29) as its main component. Evaluation of the antitrypanosomal activity of carlina oxide against *T. b. brucei* demonstrated promising results (IC_{50} = 1.0 μ g/mL), with great selectivity index values (SI = 446.0). In addition to the pure compound (main component of the *C. acaulis* EO), the authors analyzed the hexane, dichloromethane, and methanol extracts, and the two former (with considerable amount of carlina oxide (**139**)) were more active (IC_{50} = 3.7 μ g/mL (SI = 465.5) and 4.5 μ g/mL (SI = 443.3), respectively) than was the latter

(IC_{50} = 698.1 μ g/mL, SI = 1.7). When compared to the reference drug suramin (IC_{50} = 4.7 μ g/mL and SI = 280.2), carlina oxide (**139**) showed greater activity and better selectivity index. The authors suggested that the mechanism of action of carlina oxide (**139**) occurred through trypanothione reductase inhibition. The presence of the furan ring and the triple bond were considered by the authors to be important structural features for the activity and should be considered for the design of new drugs.

Kamte et al. [135] investigated the EOs of several herb species from the Apiaceae family from the Mediterranean zone (*Siler montanum* Crantz subsp. *siculum* – flowering aerial parts, *Sison amomum* L. – flowering aerial parts, *Echinophora spinosa* L. – roots and flowering aerial parts, *Kundmannia sicula* (L.) DC. – inflorescences, *Crithmum maritimum* L. – flowering aerial parts, *Helosciadium nodiflorum* (L.) Koch – whole, *Pimpinella anisum* L. – seeds, *Heracleum sphondylium* subsp. *ternatum* (Velen.) Brummit – seeds, and *Trachyspermum ammi* (L.) Sprague – seeds). The EOs from five of these plants were potent inhibitors of *T. brucei* (SaEO – 4.3 \pm 0.7 μ g/mL, EsEO roots – 2.7 \pm 0.6 μ g/mL, EsEO aerial parts – 4.0 \pm 1.6 μ g/mL, CmEO – 5.0 \pm 0.8 μ g/mL, and HnEO – 10.7 \pm 4 μ g/mL), and some of their main components were evaluated in isolation. The great potentiality of these EOs was attributed to the presence of the main constituents, considering as well the great importance of synergistic effects with minority constituents. For SaEO, the main constituents were sabinene (**17**) (54.4%), β -phellandrene (**106**) (16.6%), and germacrene D (**24**) (6.7%). For EsEO roots, they were myristicin (**140**) (41.3%), terpinolene (**141**) (22.2%), and (*Z*)-falcariol (**142**) (23.3%); for EsEO aerial parts, they were α -phellandrene (**143**) (47.2%), *p*-cymene (**11**) (25.6%), β -phellandrene (**106**) (8.3%), *E,E*-2,6-dimethyl-1,3,5,7-octatetraene (**144**) (6.3%), and α -pinene (**118**) (5.5%) (Figure 30); for CmEO, they were limonene (**8**) (38.4%), γ -terpinene (**64**) (19.9%), and sabinene (**17**) (12.4%); and for HnEO, they were myristicin (**140**) (49.1%), (*Z*)- β -ocimene (**89**) (19%), limonene (**8**) (7.8%), terpinolene (**141**) (7.1%), and germacrene D (**24**) (6.0%). With the exception of CmEO, all other active EOs showed significant selectivities against *T. brucei*, as well as good selectivity index values. For example, in their cytotoxicity evaluation performed in Balb3T3 rat fibroblasts, they found SI = 13 for *S. amomum*,

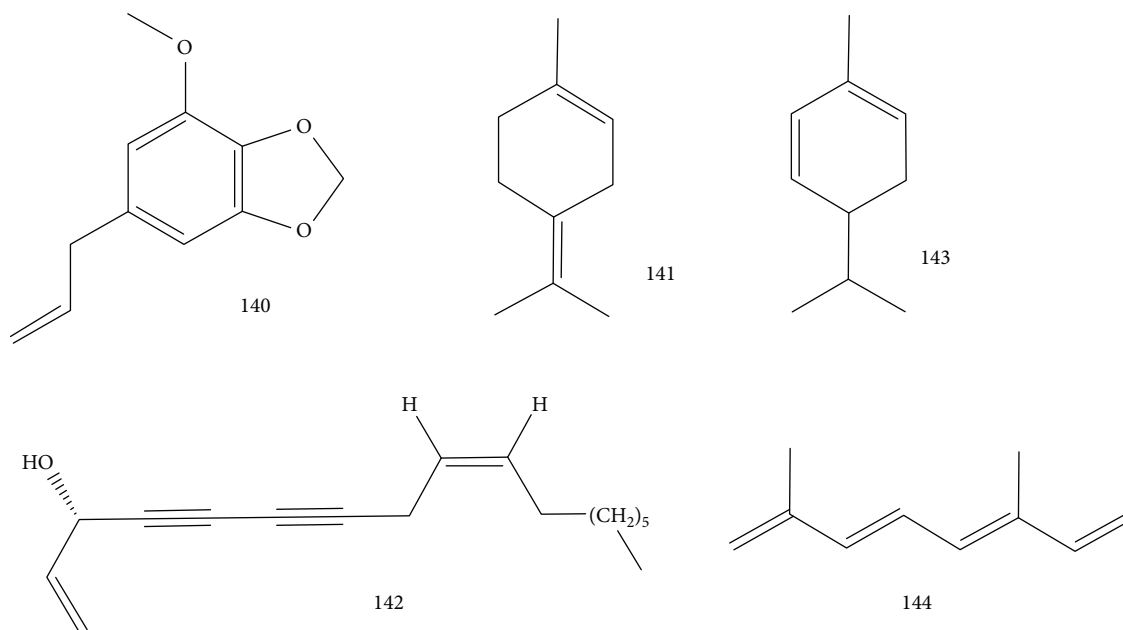


FIGURE 30: Chemical structure of myristicin (**140**), terpinolene (**141**), and (Z)-falcarinol (**142**) from aerial parts of *Echinophora spinosa* EO of α -phellandrene (**143**) and E,E-2,6-dimethyl-1,3,5,7-octatetraene (**144**) from *Crithmum maritimum* EO.

2.1 and 3.7 for *E. spinosa* roots and aerial parts, respectively, and >9.1 for *H. nodiflorum*.

The isolated components from the EOs were also evaluated by Kamte et al. [135]. Some of these showed more activity and selectivity than did their respective EOs. The most active constituents against *T. brucei* were terpinolene (**141**) ($0.035 \pm 0.005 \mu\text{g/mL}$, SI = 180), α -pinene (**118**) ($1.0 \pm 0.3 \mu\text{g/mL}$, SI > 100), β -ocimene (**89**) (EC_{50} of $1.1 \pm 0.5 \mu\text{g/mL}$, SI > 91), *p*-cymene (**11**) (EC_{50} of $4.5 \pm 1.0 \mu\text{g/mL}$, SI = 6.2), limonene (**8**) (EC_{50} of $5.6 \pm 1.6 \mu\text{g/mL}$, SI > 18), sabinene (**17**) (EC_{50} of $6.0 \pm 1.5 \mu\text{g/mL}$, SI > 17), α -phellandrene (**143**) (EC_{50} of $24 \pm 8 \mu\text{g/mL}$, SI = 4.8), and myristicin (**140**) (EC_{50} of $74 \pm 4 \mu\text{g/mL}$, SI > 1.4). As observed for the previous values, the high anti-*T. brucei* potentiality of terpinolene (**141**) should be responsible for the great EC_{50} value found in *EsEO* roots, containing these compounds as its primary constituents.

Comparison of the chemical structure of terpinolene (**141**) with other structurally similar compounds (γ -terpinene (**64**), α -phellandrene (**143**), limonene (**8**), and *p*-cymene (**11**)) highlighted the great importance of the presence of a double endocyclic and a double exocyclic bound, the latter linking the cyclohexene ring to a dimethylated carbon for the inhibition of *T. brucei* growth. This can be used as scaffold for drug design of new anti-*T. brucei* agents.

Petrelli et al. [81] evaluated EOs of many parts of *Smyrniolum olusatrum* L. (roots, leaves, flowers, and fruits), known to be rich in furan ring-containing sesquiterpenes as the main constituents. CG-MS analysis identified a domain of oxygenated sesquiterpenes (68.2% - 74.5%), followed by monoterpene hydrocarbons (13.2–22.2%) and sesquiterpene hydrocarbons (3.1–14.1%). The EO from the fruits resulted in the identification of 66 constituents, including β -acetoxyfuranoeudesm-4(15)-ene (**145**) (31.2%),

curzerene (**146**) (23.8%), isofuranodiene (**147**) (6.6%), β -phellandrene (**106**) (6.2%), and α -pinene (**118**) (5.4%). Among the flower EOs, they found 47 compounds, including curzerene (**146**) (30.5%), myrcene (**61**) (18.2%), furanoeremophil-1-one (**148**) (12.1%), germacrone (**149**) (10.4%), and isofuranodiene (**147**) (9.8%) (Figure 31). They identified 45 compounds from roots EO, including curzerene (**146**) (39.7%), furanoeremophil-1-one (**148**) (24.4%), β -phellandrene (**106**) (14.4%), and isofuranodiene (**147**) (5.8%). The EO from leaves produced 43 constituents, including furanoeremophil-1-one (**148**) (30.0%), curzerene (**146**) (24.1%), germacrone (**149**) (9.7%), β -pinene (**39**) (9.5%), and isofuranodiene (**147**) (4.8%).

These SoEOs showed effectiveness against *T. brucei brucei* with satisfactory SIs. The most powerful EO was obtained from fruits ($\text{IC}_{50} = 1.97 \pm 0.06 \mu\text{g/mL}$, SI = 29), followed by the EO from flowers ($\text{IC}_{50} = 3.0 \pm 0.4 \mu\text{g/mL}$, SI = 23) and from leaves ($\text{IC}_{50} = 3.7 \pm 0.5 \mu\text{g/mL}$, SI > 27), and at least active was the EO from roots ($\text{IC}_{50} = 4.0 \pm 0.5 \mu\text{g/mL}$, SI > 25). Some pure compounds were also tested, including isofuranodiene (**147**) ($\text{IC}_{50} = 3.0 \pm 0.8 \mu\text{g/mL}$, SI = 30), β -acetoxyfuranoeudesm-4(15)-ene (**145**) ($\text{IC}_{50} = 26 \pm 3 \mu\text{g/mL}$, SI > 3.8), and germacrone (**149**) ($\text{IC}_{50} > 100 \mu\text{g/mL}$) which had the best profiles. Taking into account that curzerene (**146**) is a thermal degradation product of isofuranodiene (**147**) [136, 137], and considering the abundance of these two constituents, it may be considered that isofuranodiene (**147**) is the major component of all SoEO and is therefore responsible for their antitrypanosomal activities. The SoEO from fruit had as its principal component β -acetoxyfuranoeudesm-4(15)-ene (**145**), also contributing to its superior potential over the other components.

Structurally, the absence of the furan ring in germacrone (**149**), as opposed to isofuranodiene (**147**)

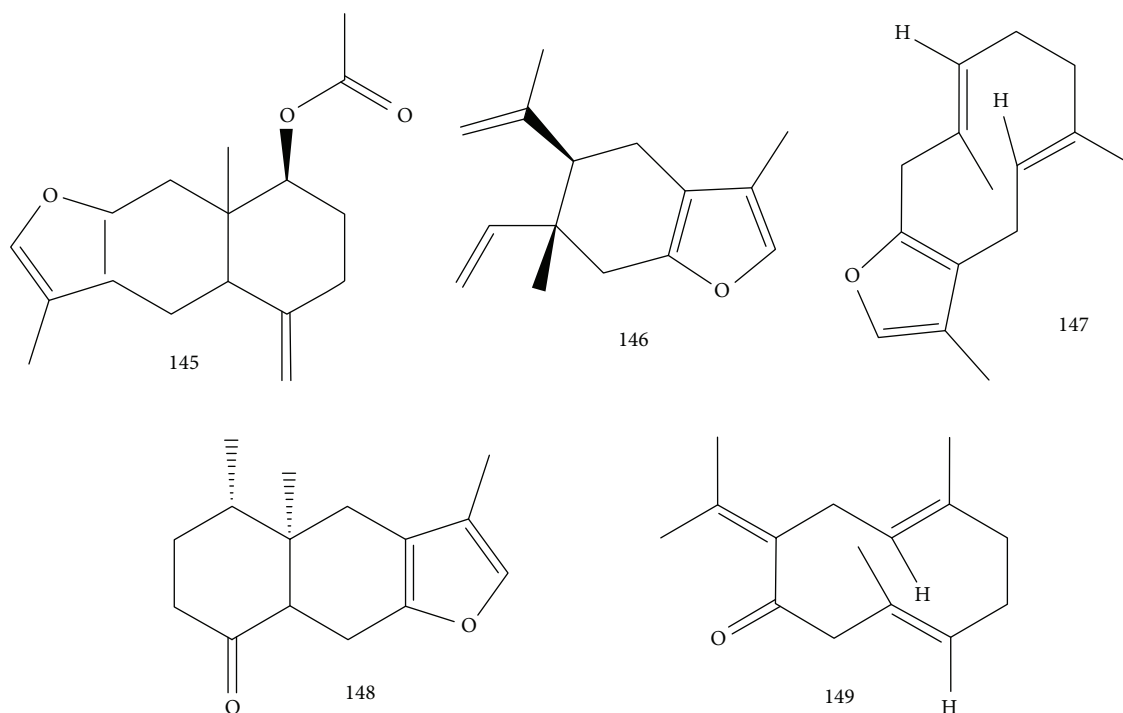


FIGURE 31: Chemical structures of β -acetoxyfuranoeudesm-4(15)-ene (**145**), curzerene (**146**), isofuranodiene (**147**), β -acetoxyfuranoeudesm-4(15)-ene (**145**), and germacrone (**149**) - main components of *Smyrniolum olusatrum* L. EO.

and β -acetoxyfuranoeudesm-4(15)-ene (**145**) structures (Figure 20), can be the main explanation of its inactivity. In addition, the more potent compound isofuranodiene (**147**) was already known for its inhibitory activity against dihydrofolate reductase, an important enzyme in purine biosynthesis and therefore in DNA synthesis. This may be the mechanism of action for its inhibition of *T. brucei* growth [138].

Muhd Haffiz and colleagues [121] evaluated the anti-*T. brucei* activity of *Cymbopogon nardus* L. (whole plant) EO and fractions, using pentamidine ($IC_{50} = 0.00438 \mu\text{g/mL}$, $SI = 4.29$) as the standard drug. CG-MS revealed that the majority of the constituents of *CnEO* were oxygenated monoterpenes (79%), sesquiterpenes (12.3%), oxygenated sesquiterpenes (2.6%), and monoterpene hydrocarbons (1.9%), including citronellal (**62**) (35.5%), geraniol (**6**) (28%), and citronellol (**51**) (11%). In the biological evaluation, *C. nardus* EO exhibited strong antitrypanosomal activity and high SI ($IC_{50} = 0.31 \pm 0.03 \mu\text{g/mL}$, $SI > 323$).

These EOs were fractionated into 7 fractions, then combined, and then refracted into 8 subfractions, and finally their activities were determined. In the great majority of cases, the fractions and subfractions showed great potential for inhibition of *T. b. brucei* growth with low cytotoxicity. The most active fractions were as follows: subfraction **4'** ($IC_{50} = 0.61 \pm 0.06 \mu\text{g/mL}$, $SI = 127$), subfraction **6'** ($IC_{50} = 0.73 \pm 0.33 \mu\text{g/mL}$, $SI \geq 137$), subfraction **7'** ($IC_{50} = 1.15 \pm 0 \mu\text{g/mL}$, $SI = 87$), and subfraction **8'** ($IC_{50} = 1.11 \pm 0.01 \mu\text{g/mL}$, $SI \geq 90$). The major constituents were γ -eudesmol (**150**) (Figure 32) and α -cadinol

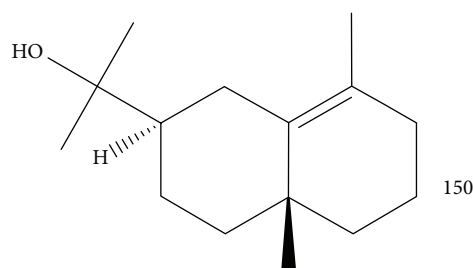


FIGURE 32: Chemical structures of γ -eudesmol (**150**) - one of the main constituents from *Cymbopogon nardus* EO.

(**53**) for subfractions **4'** and **6'** and elemol (**52**) for subfractions **7'** and **8'**.

Essential oils from aromatic and medicinal plants from Cameroon with known antitrypanosomal properties were evaluated by Kamte et al. [18]. The authors identified chemical compositions and evaluated the anti-*T. brucei* potential of the EOs and constituents from *Azadirachta indica* (leaves), *Aframomum melegueta* (seeds), *Aframomum daniellii* (leaves), *Clausena anisata* (leaves), *Dichrostachys cinerea* (seeds), and *Echinops giganteus* (roots).

For *AiEO*, 13 compounds were identified, with abundance of sesquiterpene hydrocarbons (97.4%), especially germacrene B (**151**) (74.0%) and γ -elemene (**152**) (18.3%) (Figure 33); for *AmEO*, 59 compounds were identified, with abundance of oxygenated monoterpenes (83.3%), of which 1,8-cineole (**124**) (58.5%), α -terpineol (**111**) (19.4%), and β -pinene (**39**) (7.1%) were the main constituents; for *AdEO*,

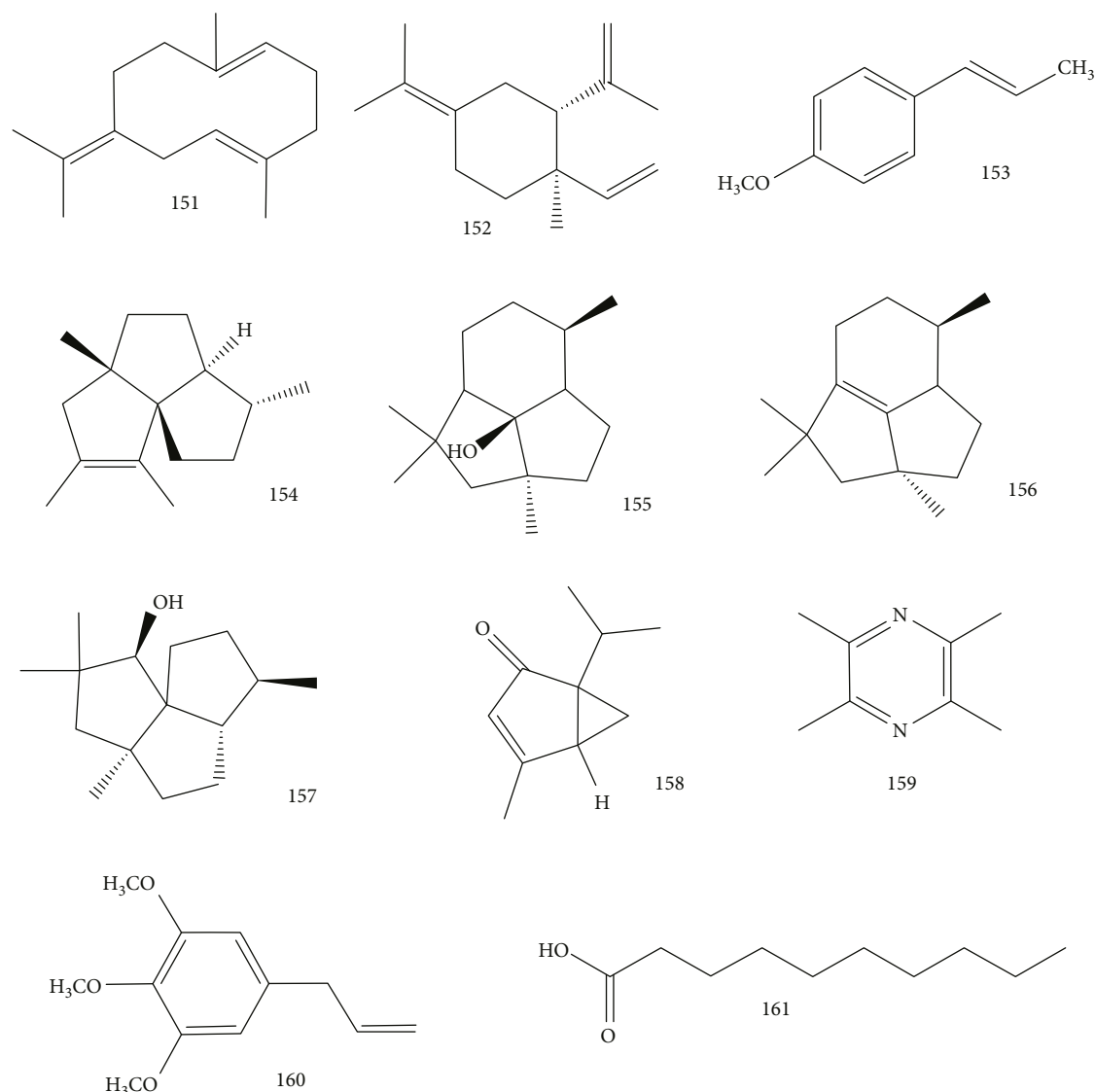


FIGURE 33: Chemical structures compounds isolated of aromatic and medicinal plants from Cameroon.

57 compounds were identified, with greater abundance of monoterpene hydrocarbons (59.8%), where sabinene (**17**) (43.9%), (*E*)-caryophyllene (**22**) (16.6%), and β -pinene (**39**) (5.8%) were the most abundant; for *CaEO*, 47 compounds were identified, with abundance of phenylpropenoids (84.0%), where (*E*)-anethole (**153**) (64.6%) and (*E*)-methyl isoeugenol (**2**) (16.1%) (Figure 33) were the main constituents; for *EgEO*, 35 compounds were identified, with abundance of sesquiterpenes (94.3%–54.7% of sesquiterpene hydrocarbons and 39.6% of oxygenated sesquiterpenes), where silphiperfol-6-ene (**154**) (23.0%), presilphiperfolan-8-ol (**155**) (22.7%), presilphiperol-7-ene (**156**) (7.8%), cameroonan-7- α -ol (**157**) (7.1%), and caryophyllene (**22**) (6.3%) were the most abundant (Figure 33); and for *D. cinereal*, 49 compounds were identified, and the class of oxygenated monoterpenes (50.6%) was the primary, and geraniol (**6**) (18.2%), terpinen-4-ol (**103**) (7.5%), linalool (**3**) (4.0%), and umbellulone (**158**) (3.8%) were the most representative constituents. Representative

amounts of other classes of compounds were also observed, especially ligustrazin (**159**) (5.1%), elemicin (**160**) (3.0%), and decanoic acid (**161**) (2.8%) (Figure 33).

The *in vitro* evaluation of these EOs demonstrated inactivity of *DcEO*, *AmEO*, and *CaEO* ($IC_{50} > 100 \mu\text{g/mL}$), and moderate activity of *AdEO* ($IC_{50} = 7.65 \pm 1.1 \mu\text{g/mL}$), *EgEO* ($IC_{50} = 10.50 \pm 1.7 \mu\text{g/mL}$), and *AiEO* ($IC_{50} = 15.21 \pm 0.97 \mu\text{g/mL}$), when compared to standard drug suramin ($IC_{50} = 0.0286 \pm 0.0008 \mu\text{g/mL}$). The SIs of the three more active EOs were also evaluated and were >13.1 , >9.52 , and >6.57 , respectively [18].

Some of the main constituents of *A. melegueta* and *A. daniellii* EOs were also evaluated. 1,8-Cineole (**124**) and terpinen-4-ol (**103**) (main compounds of *AmEO*) were inactive ($IC_{50} > 100 \mu\text{g/mL}$), while sabinene (**17**) ($IC_{50} = 5.96 \pm 1.3 \mu\text{g/mL}$), (*E*)-caryophyllene (**22**) ($IC_{50} = 8.25 \pm 1.3 \mu\text{g/mL}$), and β -pinene (**39**) ($IC_{50} = 11.4 \pm 2.6 \mu\text{g/mL}$), main components of *AdEO*, showed moderate to good anti-*T. brucei* activities [18].

1.3. Essentials Oils Active against Leishmaniasis. Leishmaniasis is a group of noncontagious infectious diseases caused by at least 20 parasitic protozoa belonging to the family Trypanosomatidae (genus *Leishmania*). It is estimated that at least 12 million people in more than 100 countries are infected, and at least another 350 million people are at risk in endemic areas [139, 140]. This set of diseases can be divided into two major groups of distinct diseases, tegumentary leishmaniasis (subdivided into cutaneous, diffuse cutaneous, and mucosal), and visceral leishmaniasis, usually more severe, with high mortality [139, 141].

The life cycle of *Leishmania* sp. begins with the blood supply of a phlebotomine that infects itself through the blood of an infected mammalian, ingesting amastigote forms of the parasite that are internalized in macrophages. In the intestine of the vector-insect, the amastigote form becomes a metacyclic promastigote form. When the insect is fed again and it bites a new mammalian, virulent promastigote forms are inoculated in the new host. In the bloodstream, they are internalized by macrophages, differentiating again into amastigotes, thus completing the cycle [140, 141].

The few therapeutic options available for treatment include a class of drugs that is more than 60 years old, the pentavalent antimonials (meglumine antimoniate and sodium stibogluconate). More recently, for the treatment of refractory and resistant cases, pentamidine, miltefosine, amphotericin B, and paromomycin are used [140].

In the same way as observed for the trypanosomiasis described above, the scarcity of drugs for leishmaniasis necessitated the use of plants, and parts of plants, as therapeutic alternatives in several parts of the world.

Between 2000 and 2018, the literature reported the use of EOs from 142 plant species (30 families) and 44 isolated compounds that were evaluated against various *Leishmania* species (*Leishmania amazonensis*, *Leishmania braziliensis*, *Leishmania aethiopica*, *Leishmania donovani*, *Leishmania chagasi*, *Leishmania infantum*, *Leishmania guyanensis*, *Leishmania panamensis*, *Leishmania mexicana*, *Leishmania tropica*, and *Leishmania major*) and forms (promastigote, axenic amastigote, and intracellular amastigote).

The most studied families were Lamiaceae, Piperaceae, and Asteraceae, with 35, 29, and 14 species evaluated, respectively. Fifty-one of the EOs (especially from plant species the families Lamiaceae and Asteraceae) and 13 isolated compounds showed IC_{50} values less than or equal to $10 \mu\text{g/mL}$ against at least one species of *Leishmania* (promastigote or amastigote forms) and were considered active based on hit selection criteria for visceral leishmaniasis [142]. In addition, four EOs and one isolated compound showed quantified activity in nanomolar concentrations, considered strongly active (Tables 1 and 2 and Figure 34) (see supplementary material Figures S1 and S2). In our review, some of the most active EOs and pure compounds were detailed for their major constituents (for EOs), efficacy (IC_{50} values), selectivity index (SI), and morphological and ultrastructure alterations in the parasite, as well as for their mechanism of action. For inactive extracts and chemical entities

($IC_{50} > 50 \mu\text{g/mL}$), and for those in which only the parasite was sensitive (moderate activity; $50 < IC_{50} > 10 \mu\text{g/mL}$), see supplementary material (Table S1).

EOs from 10 plants issued from the Sned region of Tunisia, an endemic region for various forms of *Leishmania*, showed antileishmanial activities against *L. major* and *L. infantum* promastigote forms. In general, for all tested extracts, *L. infantum* species were more sensitive than were *L. major*, and only two EOs were more effective against the parasites than were murine macrophagic cells. EOs from *Thymus hirtus* sp. *Algeriensis*, rich in oxygen-containing monoterpenes, especially linalool (**3**) (17.62%) and camphor (**14**) (13.82%), and from *Ruta chalepensis*, rich in 2-undecanone (**162**) (Figure 35) (84.28%), showed IC_{50} against *L. infantum* promastigote forms of 0.25 and $1.13 \mu\text{g/mL}$, respectively [143]. In addition, only *Thymus hirtus* sp. *Algeriensis* EO showed leishmanicidal activity against *L. major* ($IC_{50} = 0.43 \mu\text{g/mL}$). On the other hand, for these two EOs, SI values (calculated as IC_{80}/IC_{50}) ranging from 0.19 to 1.57 showed inadequate antileishmanial activity by hit selection [143]. Two other EOs (from *T. articulata* and *Lavandula multifida*) were inactive against *L. major* promastigotes, and for the remaining six EOs, IC_{50} values ranged from 0.30 to $2.23 \mu\text{g/mL}$, but with high levels of cytotoxicity ($SI < 1$) [143].

EOs from sixteen plant species belonging to various families, purchased from QUINARI Cosmetic and Fragrances Inc. (Maringá, Pr, Brazil) or collected in Lavras, MG (Brazil), were evaluated for their biological potential against *L. amazonensis* promastigote forms after 24 h of exposure [144]. None of the EOs tested showed desirable IC_{50} values. For the four most effective EOs (from *Matricaria chamomilla*, *Cordia verbenaceae*, *Siparuna guianensis*, and *Cinnamodendron dinisii* species), the IC_{50} values ranged from 48.55 to $64.75 \mu\text{g/mL}$ and were considered moderately active or inactive. Furthermore, for all EOs tested, SI were not satisfactory ($0.99 < SI > 3.94$). From the chemical composition of the evaluated EOs and the IC_{50} and SI values, the authors compared these leishmanicidal activities and cytotoxicities with those of EOs from other plant species. Literature reports that EOs from *Matricaria chamomilla* showed no leishmanicidal activity against *L. donovani* specie. Another EO from *Lantana camara*, with similar major constituents (farnesene (**117**) derivatives as major constituents), showed significant leishmanicidal activity against *L. amazonensis* ($IC_{50}/72 \text{ h} = 0.25 \mu\text{g/mL}$), but with high cytotoxicity [145, 146]. In another example, EO from *Bulnesia sarmientoi*, with 48.29% of guaiol (**163**) (Figure 35) as its major constituent, was inactive against *L. amazonensis* ($IC_{50} = 85.56 \mu\text{g/mL}$). However, EO from *Endlicheria bracteolate*, with 72.12% of guaiol (**163**), had an IC_{50} of $7.93 \mu\text{g/mL}$ against the same *Leishmania* species and a similar value of SI (1.91) [147]. Finally, they observed that the concentration of linalool (**3**) in the EO from *Salvia sclarea* was insufficient to promote leishmanicidal activity for this EO, since Kuźma et al. demonstrated that linalool-rich EO from the leaves of *Croton cajucara* promoted morphological changes in *L. amazonensis* promastigotes treated at concentrations of 15 ng/mL [148].

TABLE 1: Active EOs against *Leishmania* species.

Plant family	Plant specie	Plant origin	Part of plant	Major constituents (%)	LC ₅₀ / <i>Leishmania</i> specie (evolutionary form)	SI	Ref.
Rutaceae	<i>Ruta chalepensis</i>	Tunisia/Sned region	Aerial parts	2-Undecanone (162) (84.28%)	8.16 µg.mL ⁻¹ / <i>L. major</i> (promastigote) 1.13 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote)	1.57 for <i>L. major</i> and 2.7 for <i>L. infantum</i> ^a	[143]
Umbelliferae	<i>Pituranthos tortuosus</i>	Tunisia/Sned region	Aerial parts	nd	0.64 µg.mL ⁻¹ / <i>L. major</i> (promastigote) 0.66 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote)	0.78 for <i>L. major</i> and 0.76 for <i>L. infantum</i> ^a	[143]
Cyperaceae	<i>Cyperus rotundus</i>	Tunisia/Sned region	Aerial parts	nd	1.40 µg.mL ⁻¹ / <i>L. major</i> (promastigote) 0.55 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote)	0.09 for <i>L. major</i> and 0.23 for <i>L. infantum</i> ^a	[143]
Cupressaceae	<i>Tetraclinis articulata</i>	Tunisia/Sned region	Aerial parts	nd	>8 µg.mL ⁻¹ / <i>L. major</i> (promastigote) 3.31 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote)	0.25 for <i>L. major</i> and 0.6 for <i>L. infantum</i> ^a	[143]
Pinaceae	<i>Pinus halepensis</i>	Tunisia/Sned region	Aerial parts	nd	2.23 µg.mL ⁻¹ / <i>L. major</i> (promastigote) 1.92 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote)	0.61 for <i>L. major</i> and 0.94 for <i>L. infantum</i> ^a	[143]
Fabaceae	<i>Copaifera reticulata</i>	Brazil/Pará State	Trunks	β-Caryophyllene (22) (40.9%)	5.0 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) 15.0 µg.mL ⁻¹ / <i>L. amazonensis</i> (axenic amastigote) 20.0 µg.mL ⁻¹ / <i>L. amazonensis</i> (intracellular amastigote)	8.0 for promastigote and 2.5 for axenic amastigote	[153]
	<i>Copaifera multijuga</i>	Brazil/Amazonas State	Trunks	β-Caryophyllene (22) (57.5%) Copalic acid (164) (6.2%)	10.0 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) 7.2 µg/mg/ <i>L. amazonensis</i> (axenic amastigote)	nd	[153]
	<i>Vouacappoua americana</i>	French Guiana	Wood	nd		5.0	[190]
	<i>Copaifera</i> ssp. (C1) commercial oil	Brazil/Acre State	nd	<i>trans</i> -β-Caryophyllene (22) (44.23%) α-Humulene (136) (7.29) Caryophyllene oxide (38) (10.17)	2.9 µg.mL ⁻¹ / <i>L. amazonensis</i> (amastigote)	29.3	[157]
	<i>Copaifera</i> ssp. (C4) commercial oil	Brazil/Pará State	nd	<i>trans</i> -β-Caryophyllene (22) (36.46%) Copalic acid (164) (7.62%) Germacrene D (24) (4.56%)	2.3 µg.mL ⁻¹ / <i>L. amazonensis</i> (amastigote)	40.1	[157]
Lamiaceae	<i>Satureja punctata</i>	Inchini/Addis Abada	Leaves	Geraniol (6) (27.62%) Neral (7) (21.72%) α-Bisabolol (165) (13.62%)	156.5 µg.mL ⁻¹ / <i>L. donovani</i> (promastigote) 312.5 µg.mL ⁻¹ / <i>L. aethiopia</i> (promastigote) 8.70 µg.mL ⁻¹ / <i>L. donovani</i> (axenic amastigote)	0.001 for <i>L. donovani</i> and 0.05 for <i>L. aethiopia</i>	[159]

TABLE 1: Continued.

Plant family	Plant specie	Plant origin	Part of plant	Major constituents (%)	LC ₅₀ /Leishmania specie (evolutionary form)	SI	Ref.
<i>Thymus hirtus</i> sp. Algeriensis	Tunisia/Sned region	Aerial parts	Linalool (3) (17.62%)	4.06 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. aethiopica (axenic amastigote)	0.19 for L. major and 1.34 for L. infantum ^a	[143]	
			Camphor (14) (13.82%)				
			Terpinen-4-ol (103) (6.80%)				
<i>Rosmarinus o. cinalis</i>	Tunisia/Sned region	Aerial parts	nd	>8 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote)	0.09 for L. major and 0.23 for L. infantum ^a	[143]	
			nd	3.05 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. infantum (promastigote)			
<i>Teucrium alopecurus</i>	Tunisia/Sned region	Aerial parts	nd	1.14 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote)	0.05 for L. major and 0.21 for L. infantum ^a	[143]	
<i>Lavandula multifida</i>	Tunisia/Sned region	Aerial parts	nd	>8 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote)	nd	[143]	
<i>Lavandula stoechas</i>	Morocco/Province of Quezzane	Aerial parts	Fenchone (166) (31.81%) Camphor (14) (29.60%) Terpineol (111) (13.1%)	0.9 $\mu\text{g}/\text{mL}$ /L. major (promastigote) 7 $\mu\text{g}/\text{mL}$ /L. infantum (promastigote)	nd	[171]	
<i>Origanum compactum</i> Benth	Morocco/Province of Quezzane	Aerial parts (vegetative, flowering and post-flowering)	P-Cymene (11) (17.81–19.24%) Thymol (1) (15.32–38.01%) Carvacrol (10) (6.39–43.58%)	0.13–0.26 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote) 0.02–0.12 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. infantum (promastigote) 0.22–0.72 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. tropica (promastigote)	nd	[173]	
<i>Mentha pulegium</i>	Morocco/Province of Quezzane	Aerial parts	Pulegone (128) (40.98%) Menthone (132) (21.164%)	1.3 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote) 2 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. infantum (promastigote) 2.2 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. tropica (promastigote)	nd	[172]	
<i>Rosmarinus o. cinalis</i>	Morocco/Province of Quezzane	Aerial parts	1,8-Cineole (124) (23.673%) Camphor (14) (18.743%) Borneol (112) (15.46%)	2.6 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote) 1.2 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. infantum (promastigote) 3.5 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. tropica (promastigote)	nd	[172]	
<i>Tetradenia riparia</i>	Brazil/Paraná State	Leaves	Summer Fenchone (166) (5.54%) α -Cadinol (53) (16.91%) 14-Hydroxy-9-epi-caryophyllene (167) (15.28%);	15.67 ng·mL ⁻¹ /L. amazonensis (promastigote)	Summer 94.19	[191]	

TABLE 1: Continued.

Plant family	Plant specie	Plant origin	Part of plant	Major constituents (%)	LC ₅₀ / <i>Leishmania</i> specie (evolutive form)	SI	Ref.														
Asteraceae	<i>Tetradenia riparia</i>	Brazil/Paraná State	Leaves	Winter α -Cadinol (53) (14.82%) 14-Hydroxy-9-epi-caryophyllene (167) (10.23%) Dehydroroyleanone (168) (20.47%) Autumn α -Cadinol (53) (17.16%) 14-Hydroxy-9-epi-caryophyllene (167) (13.10%) Dehydroroyleanone (168) (16.50%). Spring α -Cadinol (53) (13.81%) 14-Hydroxy-9-epi-caryophyllene (167) (12.70%) 6,7-Dehydroroyleanone (168) (12.51%)	Winter 13.31 ng.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) Autumn 15.66 ng.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) Spring 15.47 ng.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	Winter 76.80 Autumn 25.01 Spring 67.51	[192]														
								<i>Tetradenia riparia</i>	Brazil/Paraná State	Leaves	nd	0.03 μ g.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	5.67	[192]							
															<i>Tetradenia riparia</i>	Brazil/Paraná State	Leaves	nd	30.0 μ g.mL ⁻¹ / <i>L. amazonensis</i> (intracellular amastigote)	nd	[175]
								<i>Teucrium polium</i>	Northern Tunisia	Aerial parts	Caryacrol (10) (56.06%) β -Caryophyllene (22) (7.68%) α -Pinene (118) (5.02%)	0.09 μ g.mL ⁻¹ / <i>L. infantum</i> (Promastigotes) 0.15 μ g.mL ⁻¹ / <i>L. major</i> (promastigotes)	40.44 for <i>L. infantum</i> and 24.26 for <i>L. major</i>	[174]							
															<i>Salvia o cinalis</i>	Northern Tunisia	Aerial parts	nd	2.67 μ g.mL ⁻¹ / <i>L. infantum</i> (Promastigote) 3.4 μ g.mL ⁻¹ / <i>L. major</i> (promastigote)	7.54 for <i>L. infantum</i> and 5.92 for <i>L. major</i>	[174]
								<i>Thymus hirtus</i>	Northern Tunisia	Aerial parts	α -Pinene (118) (16.93%)	5.90 μ g.mL ⁻¹ / <i>L. infantum</i> (Promastigote) 8.8 μ g.mL ⁻¹ / <i>L. major</i> (promastigote)	24.78 for <i>L. infantum</i> and 16.61 for <i>L. major</i>	[174]							
															<i>Artemisia absinthium</i> L.	Inchini/Addis Abada	Leaves	Camphor (14) (27.40%) Davanone (169) (16.43%) Ethyl(<i>B</i>)-cinnamate (170) (5.81%)	0.15 μ g.mL ⁻¹ / <i>L. donovani</i> (promastigote) 0.15 μ g.mL ⁻¹ / <i>L. aethiopica</i> (promastigote) 42.0 μ g.mL ⁻¹ / <i>L. donovani</i> (axenic amastigote) 7.94 μ g.mL ⁻¹ / <i>L. aethiopica</i> (axenic amastigote)	3.6 for <i>L. donovani</i> and 19.2 for <i>L. aethiopica</i>	[158]
								<i>Echinops kebericho</i> Mesfin	Inchini/Addis Abada	Tubers	Dehydrocostus lactone (171) (41.83%)	0.07 μ g.mL ⁻¹ / <i>L. donovani</i> (promastigote) 0.00097 μ g.mL ⁻¹ / <i>L. aethiopica</i>	0.8 for <i>L. donovani</i> and 1.7 for <i>L. aethiopica</i>	[158]							

TABLE 1: Continued.

Plant family	Plant specie	Plant origin	Part of plant	Major constituents (%)	LC ₅₀ /Leishmania specie (evolutionary form)	SI	Ref.
	<i>Achillea millefolium</i>	Brazil/Paraná State	Leaves and flowers	nd	(promastigote) 0.50 µg.mL ⁻¹ /L. donovani (axenic amastigote) 0.24 µg.mL ⁻¹ /L. aethiopica (axenic amastigote) 7.8 µg.mL ⁻¹ /L. amazonensis (promastigote) 6.5 µg.mL ⁻¹ /L. amazonensis (intracellular amastigote)	9.2 for promastigote and 11.0 for intracellular amastigote	[161]
	<i>Matricaria chamomilla</i>	USA/Clackamas	Flowers	nd	10.30 µg.mL ⁻¹ /L. braziliensis (intracellular amastigote) 2.87 µg.mL ⁻¹ /L. panamensis (intracellular amastigote) 230 µg.mL ⁻¹ /L. braziliensis (axenic amastigote)	2.93 for L. braziliensis intracellular amastigote, 10.52 for L. panamensis intracellular amastigote, and 0.14 for L. braziliensis axenic amastigote	[193]
	<i>Pulicaria gnaphalodes</i>	Iran/Tabas region	Aerial parts	1,8-Cineole (124) (9.45%) α-Pinene (118) (3.81%) α-Terpineol (111) (3.63%)	0.27 µg.mL ⁻¹ /L. major (promastigote)	nd	[194]
	<i>Vanillosnopsis arborea Baker</i>	Brazil/Ceará State	Stems	α-Bisabolol (165) (97.9%) o-Methyl eugenol (172) (1.6%) Bisabolol oxide (173) (0.5%)	7.35 µg.mL ⁻¹ /L. amazonensis (promastigote) 12.58 µg.mL ⁻¹ /L. amazonensis (intracellular amastigote)	11.52	[183]
	<i>Artemisia herba alba</i>	Northern Tunisia	Aerial parts	nd	1.22 µg.mL ⁻¹ /L. infantum (promastigote) 2.78 µg.mL ⁻¹ /L. major (promastigote)	7.21 for L. infantum and 3.16 for L. major	[174]
	<i>Artemisia campestris</i>	French Guiana	Leaves	α-Pinene (118) (24.98%)	3.24 µg.mL ⁻¹ /L. infantum (promastigote) 4.59 µg.mL ⁻¹ /L. major (promastigote)	24.87 for L. infantum and 17.55 for L. major	[174]
	<i>Mikania micrantha</i>	Jamia Hamdard	Leaves	Camphor (14) (52.06%) β-Caryophyllene (22) (10.95%) 1,8-Cineole (124) (5.57%)	6.8 µg.mL ⁻¹ /L. amazonensis (axenic amastigote) 14.63 µg.mL ⁻¹ /L. donovani (promastigote) 7.3 µg.mL ⁻¹ /L. donovani (intracellular amastigote)	7.0	[190]
	<i>Artemisia annua</i>	Brazil/São Luis State	Leaves	Curzerene (146) (47.3%) γ-Elemene (152) (14.25%) trans-β-Elemenone (174) (10.4%)	3.04 µg.mL ⁻¹ /L. amazonensis (promastigote) 1.92 µg.mL ⁻¹ /L. amazonensis (amastigote)	14.9 for promastigote and 23.9 for amastigote	[163]
Myrtaceae	<i>Myrtus communis</i>	Tunisia/Sned region	Aerial parts	α-Pinene (118) (52.52%)	4.58 µg.mL ⁻¹ /L. infantum (promastigote) 6.28 µg/mL/L. major (promastigote)	27.86 for L. infantum and 20.31 for L. major	[174]
			Aerial parts	nd			[143]

TABLE 1: Continued.

Plant family	Plant specie	Plant origin	Part of plant	Major constituents (%)	LC ₅₀ /Leishmania specie (evolutionary form)	SI	Ref.
	<i>Eucalyptus globulus</i>				0.98 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. major (promastigote) 0.68 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. infantum (promastigote)	0.27 for L. major and 0.38 for L. infantum ^a	
	<i>Myrtus communis</i>	Kerman province	Leaves	α -Pinene (118) (24.7%) 1,8-Cineole (124) (19.6%) Linalool (3) (12.6%)	8.4 $\mu\text{g}/\text{mL}$ /L. tropica (promastigote) 11.6 $\mu\text{g}/\text{mL}$ /L. tropica (amastigote)	11.7	[195]
Euphorbiaceae	<i>Croton cajucara</i>	Brazil/Amazonas State	Leaves	Linalool (3)	8.3 $\text{ng}\cdot\text{mL}^{-1}$ /L. amazonensis (promastigote) 15.5 $\text{ng}\cdot\text{mL}^{-1}$ /L. amazonensis (amastigote)	nd	[162]
	<i>Croton pedicellatus</i>	Tolima	Leaves	Borneol (112) γ -Terpinene (64) Germacrene D (24) trans- β -Caryophyllene (22)	46.68 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. panamensis (amastigote) 7.14 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. panamensis (promastigote) 19.77 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. braziliensis (amastigote) 19.65 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. braziliensis (promastigote)	0.83 for L. panamensis (amastigotes), 1.30 for L. panamensis (promastigotes), 0.47 for L. braziliensis (amastigotes), and 0.47 for L. braziliensis (promastigotes)	[196]
	<i>Cymbopogon citratus</i>	Brazil/Paraná State	Leaves	Citral (63) Geranial (6) (42.2%) Neral (7) (36.3%)	1.7 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. amazonensis (promastigote) 3.2 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. amazonensis (amastigote)	14.7 for promastigote and 7.8 for amastigote	[167]
	<i>Cymbopogon citratus</i>	French Guiana	Leaves	nd	5.3 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. amazonensis (axenic amastigote)	5.0	[188]
Piperaceae	<i>Piper angustifolium Lam.</i>	Brazil/Mato Grosso do Sul State	Leaves	Spathulenol (108) (23.78%) Caryophyllene oxide (38) (13.06%)	1.43 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. infantum (intracellular amastigote)	22.15	[170]
	<i>Piper hispidum (Piperaceae)</i>	French Guiana	Leaves	Curzerene (146) (15.7%), Germacrene B (151) (10.9%) α -Selinene (175) (10.5%)	3.4 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. amazonensis (axenic amastigote) 4.7 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. amazonensis (intracellular amastigote)	11.0 for axenic amastigote and 8.0 for intracellular amastigotes-	[188]
Annonaceae	<i>Annona foetida</i>	Brazil/Amazonas State	Leaves	Bicyclogermacrene (23) (35.12%) (E)-Caryophyllene (22) (14.19%) α -Copaene (113) (8.19%)	16.2 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. amazonensis (promastigote) 9.9 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. braziliensis (promastigote) 27.2 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. chagasi (promastigote) 4.1 $\mu\text{g}\cdot\text{mL}^{-1}$ /L. guyanensis (promastigote)	nd	[197]
	<i>Xylopia discreta</i>	Colombia/Municipality of Barrancabermeja	Leaves	α - and β -Pyrene (176) Camphene (15) β -Myrcene (61) 1,8-Cineol (128)	EC ₅₀ = 6.3 ^b and 6.25 ^c $\mu\text{g}\cdot\text{mL}^{-1}$ /L. panamensis (promastigote) ^b	11.0 ^b and 25.6 ^c	[198]

TABLE 1: Continued.

Plant family	Plant specie	Plant origin	Part of plant	Major constituents (%)	LC ₅₀ /Leishmania specie (evolutionary form)	SI	Ref.
Verbenaceae	<i>Lippia citriodora</i>	Antioquia	Aerial parts	Limonene (8) (8.4%) Neral (7) (15.0%) Geraniol (6) (17.5%)	5.2 µg.mL ⁻¹ /L. <i>chagasi</i> (promastigote)	nd	[56]
	<i>Lippia origanoides</i>	Cauca/Mercaderes	Aerial parts	p-Cymene (11) (11.5%) Thymol (1) (53.6%)	4.4 µg.mL ⁻¹ /L. <i>chagasi</i> (promastigote)	nd	[56]
	<i>Lantana camara</i>	Brazil/Minas Gerais State	Leaves	Germacrene-D (24) (24.90%) (E)-Caryophyllene (22) (14.31%) (E,E)-Farnesene (117) (11.58%)	0.25 µg.mL ⁻¹ /L. <i>amazonensis</i> (promastigote) 18 µg.mL ⁻¹ /L. <i>chagasi</i> (promastigote)	LC ₅₀ 10 µg/mL and CC ₅₀ 4 µg/mL	[145]
Apiaceae	<i>Fenula communis</i>	Northern Tunisia	Aerial parts	β-Caryophyllene (22) (15.22%) Myrcene (61) (10.33%) α-Eudesmol (177) (9.8%)	0.05 µg.mL ⁻¹ /L. <i>infantum</i> (promastigote) 0.11 µg.mL ⁻¹ /L. <i>major</i> (promastigote)	81.60 for L. <i>infantum</i> 37.09 for L. <i>major</i>	[174]
Geraniaceae	<i>Pelargonium graveolens</i>	Northern Tunisia	Aerial parts	Citronellol (51) (24.75%) Geraniol (6) (13.99%) γ-Eudesmol (150) (11.23%)	0.11 µg.mL ⁻¹ /L. <i>infantum</i> (promastigote) 0.28 µg.mL ⁻¹ /L. <i>major</i> (promastigote)	57.36 for L. <i>infantum</i> 22.53 for L. <i>major</i>	[174]
Burseraceae	<i>Protium ovatum</i> <i>Protium heptaphyllum</i>	Brazil/Goiás State French Guiana	Leaves Fruits	Spathulenol (108) (17.6%) Caryophyllene oxide (38) (16.4%) β-Caryophyllene (22) (14.0%)	2.28 µg.mL ⁻¹ /L. <i>amazonensis</i> (promastigote) 3.7 µg.mL ⁻¹ /L. <i>amazonensis</i> (axenic amastigote)	nd 19.0	[199] [188]
Scrophulariaceae	<i>Achetaria guianensis</i>	French Guiana	Leaves and stems	nd	6.3 µg.mL ⁻¹ /L. <i>amazonensis</i> (axenic amastigote) 0.7 µg.mL ⁻¹ /L. <i>amazonensis</i> (axenic amastigote)	5.0	[188]
Plantaginaceae	<i>Otacanthus azureus</i>	French Guiana	Aerial parts	nd	16.1 µg.mL ⁻¹ /L. <i>amazonensis</i> (intracellular amastigote)	51.0 for axenic amastigote and 2.0 for intracellular amastigote	[188]
Chenopodiaceae	<i>Chenopodium ambrosioides</i>	Havana City	Aerial parts	Carvacrol (10) (62.36%) Ascaridole (37) (22.54%)	EC ₅₀ = 3.7 µg.mL ⁻¹ /L. <i>amazonensis</i> (promastigote) EC ₅₀ = 4.6 µg.mL ⁻¹ /L. <i>amazonensis</i> (amastigote)	15.0	[120]
	<i>Chenopodium ambrosioides</i>	Havana City	Aerial parts	nd	EC ₅₀ = 4.45 µg.mL ⁻¹ /L. <i>donovani</i> (promastigote) EC ₅₀ = 5.14 µg.mL ⁻¹ /L. <i>donovani</i> (amastigote)	nd	[177]
	<i>Chenopodium ambrosioides</i>	Havana City	Aerial parts	nd	3.74 µg.mL ⁻¹ /L. <i>amazonensis</i> (promastigote)	nd	[176]
Bixaceae	<i>Bixa orellana</i> L.	Havana City	Fruits	Ishwarane (178) (18.6%) Geranylgeraniol (5) (9.1%) Bicyclogermacrene (23) (8.4%)	8.54 µg.mL ⁻¹ /L. <i>amazonensis</i> (amastigote)	7.0	[181]

^aSI calculated as IC₈₀/IC₅₀. ^bMurine infection assay (J774 cells infected with L. *panamensis*). ^cHuman infection assay (U937 cells infected with L. *panamensis*). nd: not determined.

TABLE 2: Active and inactive isolated compounds and/or synthesized derivatives from EOs actives against *Leishmania* species.

Classes	Name and/or chemical structure of isolated or synthesized compound	Activity (IC ₅₀)/ <i>Leishmania</i> specie (evolutive form)	SI	Ref.
Monoterpene hydrocarbon	3-Carene (119)	72.5 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	nd	[187]
	<i>p</i> -Cymene (11)	>1000 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	nd	[187]
	α -Pinene (118)	19.7 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) 16.1 µg.mL ⁻¹ / <i>L. amazonensis</i> (axenic amastigote) 15.6 µg.mL ⁻¹ / <i>L. amazonensis</i> (intracellular amastigote)	21.5 for promastigote, 26.4 for axenic amastigote, and 27.2 for intracellular amastigote	[169]
Oxygenated monoterpene	Carvacrol (10)	25.4 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	nd	[187]
	Thymol (1)	26.8 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) 9.8 µg.mL ⁻¹ / <i>L. chagasi</i> (promastigote)	nd	[187, 200]
	(-)-Carvone (13)	194.7 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	nd	[187]
	(-)-Menthol (130)	198.9 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	nd	[187]
	1,8-Cineole (124)	568.1 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote)	nd	[187]
	Linalool (3)	550 µg.mL ⁻¹ / <i>L. infantum chagasi</i> (axenic amastigote) 276.2 µg.mL ⁻¹ or 8.3 ng.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) 15.5 ng.mL ⁻¹ / <i>L. amazonensis</i> (amastigote)	nd	[162] [187] [166]
	Citral (63)	8.0 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigotes) 25.0 µg.mL ⁻¹ / <i>L. amazonensis</i> (amastigotes)	6.3 for promastigote and 2.0 for amastigote	[167]
	Geraniol (9)	3.78 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote) 5.57 µg.mL ⁻¹ / <i>L. major</i> (promastigote)	21.26 for <i>L. infantum</i> 14.43 for <i>L. major</i>	[174]
	Camphor (14)	5.55 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote) 7.90 µg.mL ⁻¹ / <i>L. major</i> (promastigote)	4.56 for <i>L. infantum</i> 3.20 for <i>L. major</i>	[174]
	Carvacrol (10)	7.35 µg.mL ⁻¹ / <i>L. infantum</i> (promastigote) 9.15 µg.mL ⁻¹ / <i>L. major</i> (promastigotes) 2.3 µg.mL ⁻¹ / <i>L. chagasi</i> (promastigote)	34.08 for <i>L. infantum</i> and 27.37 for <i>L. major</i>	[174, 200]
	Ascaridole (37)	0.1 µg.mL ⁻¹ / <i>L. amazonensis</i> (promastigote) 0.3 µg.mL ⁻¹ / <i>L. amazonensis</i> (amastigote)	4.0	[64]

TABLE 2: Continued.

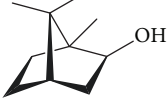
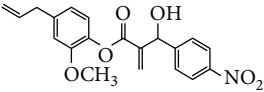
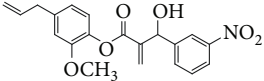
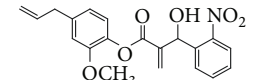
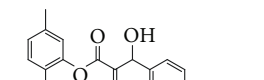
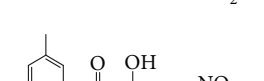
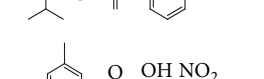
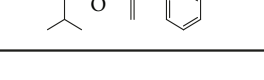
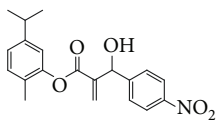
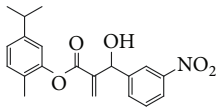
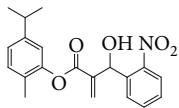
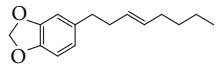
Classes	Name and/or chemical structure of isolated or synthesized compound	Activity (IC ₅₀)/ <i>Leishmania</i> specie (evolutive form)	SI	Ref.
Oxygenated sesquiterpene	(-)- α -Bisabolol (165)	10.99 $\mu\text{g.mL}^{-1}$ / <i>L. infantum</i> (promastigote) 4.95 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigote)	9.38 for <i>L. amazonensis</i>	[183, 185]
	Caryophyllene Oxide (38)	4.9 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigote) 13.6 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (amastigote)	1.0	[64]
	β -Caryophyllene (22)	1.3 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (amastigote) 1.06 $\mu\text{g.mL}^{-1}$ / <i>L. infantum</i> (promastigote) 1.33 $\mu\text{g.mL}^{-1}$ / <i>L. major</i> (promastigote)	48.9 for <i>L. amazonensis</i> , 20.82 for <i>L. infantum</i> , and 16.59 for <i>L. major</i>	[174]
	Phenolic compounds	Eugenol (2)	220 $\mu\text{g.mL}^{-1}$ / <i>L. infantum</i> (promastigote) 500 $\mu\text{g.mL}^{-1}$ / <i>L. infantum chagasi</i> (axenic amastigote) 82.9 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigote)	nd
Phenylpropanoid	Isoborneol (179) 	190.2 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigote)	nd	[187]
Diterpene	6,7-Dehydroroyleanone (167) 	$\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigote)	0.22	[192]
Others		8.75 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	>45.71	[186]
		10.49 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	>38.13	[186]
		4.71 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	>84.92	[186]
		11.40 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	nd	[186]
		10.56 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	nd	[186]
		5.91 $\mu\text{g.mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	nd	[186]

TABLE 2: Continued.

Classes	Name and/or chemical structure of isolated or synthesized compound	Activity (IC ₅₀)/ <i>Leishmania</i> specie (evolutive form)	SI	Ref.
		18.08 $\mu\text{g}\cdot\text{mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	nd	[186]
		22.30 $\mu\text{g}\cdot\text{mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	nd	[186]
		13.60 $\mu\text{g}\cdot\text{mL}^{-1}$ / <i>L. amazonensis</i> (promastigotes)	nd	[186]
	 5-[(3 <i>E</i>)-Oct-3-en-1-yl]-1,3-benzodioxole	82.5 $\mu\text{g}\cdot\text{mL}^{-1}$ / <i>L. infantum</i> (promastigotes)	2.4	[186]

nd: not determined.

In order to explore ethnopharmacological data of copaiba oils obtained from Peru, Maranhão, and Amazonas (states in Brazil) and French Guiana which are used in folk medicine to treat leishmaniasis [149–152], Santos and coworkers investigated the antiproliferative effect of EOs from eight kinds of Brazilian copaiba against promastigote and amastigote forms of *L. amazonensis* [153]. All copaiba oils showed some level of activity with IC₅₀ values ranging between 5.0 and 22.0 $\mu\text{g}/\text{mL}$. The most active EO (from *Copaifera reticulata*, IC₅₀ = 5.0 $\mu\text{g}/\text{mL}$) demonstrated effects against axenic and intracellular amastigote forms, with IC₅₀ values of 15.0 and 20 $\mu\text{g}/\text{mL}$, respectively. With respect to cytotoxicity, this same EO showed a tolerable value of SI (8.0) to promastigote forms and an inadequate value (2.5) to axenic amastigote forms. Nevertheless, studies revealed that copaiba oil from *Copaifera reticulata* did not alter the viability of peritoneal macrophages at a concentration of 500 $\mu\text{g}/\text{mL}$, and the treatment at 500 mg/kg with EOs from *Copaifera reticulata* and *Copaifera multijuga* did not induce behavioral alterations, lesions, or bleeding in the stomachs of mice [154, 155].

These results involving copaiba EOs from various species led the same authors to investigate the *in vivo* antileishmanial activity against *L. amazonensis* of an EO from *Copaifera martii*, also using electron microscopy, biochemical analysis, and flow cytometry [156]. Infected mice were treated with copaiba oil for 30 days. After oral treatment (100 mg/kg/day), oral and topical (1 mg/mm²) treatments reduced the average lesion size in relation to the control group (75% and 72.5% reduction, respectively); however, no significant difference was observed when compared to the reference drug glucantime (79.5% reduction). Nevertheless, topical and subcutaneous (100 mg/kg/day) treatments did not show significant reduction in average lesion size, and the subcutaneous treatment caused injuries to the animal.

Histopathological and mutagenicity evaluations showed no genotoxic effects or changes in various organs in animals treated with copaiba EO compared with control animals. In addition, the following microscopic aspects of the parasite were observed: (i) promastigote forms of *L. amazonensis* treated with concentrations of 14 $\mu\text{g}/\text{mL}$ (IC₅₀) and 70 $\mu\text{g}/\text{mL}$ (IC₉₀) showed ultrastructural changes and swollen mitochondria, and (ii) an increase in plasma membrane permeability and depolarization of the mitochondrial membrane potential were observed in axenic amastigotes treated with 100 and 200 $\mu\text{g}/\text{mL}$ (Figure 1). These results supported the notion that copaiba oil may be the source of a new drug; however, its mechanism of action still needs to be clarified [156].

The antileishmanial effects of copaiba EOs from *Copaifera reticulata* and *Copaifera martii* species against *L. amazonensis* led another research group to investigate the biological potential of four commercial oils from *Copaifera* ssp. C1–C4, β -caryophyllene-, sesquiterpene- and diterpene-rich fractions were obtained from distillation [157]. Diterpene-rich EOs (C2 and C3) were more active against *L. amazonensis* promastigotes. Sesquiterpene-rich EOs C1 and C4 were more potent against intracellular amastigotes, with IC₅₀ of 2.9 and 2.3 $\mu\text{g}/\text{mL}$, respectively. In comparison with the same activity of EO from *Copaifera reticulata* [153], C1 and C4 EOs were 6.9- and 8.7-fold more potent, respectively. For all the compared EOs containing β -caryophyllene (22) as their major constituent, the good IC₅₀ value (1.3 $\mu\text{g}/\text{mL}$ or 6.4 μM) demonstrated by the isolated sesquiterpene suggested that this compound may directly influence the antileishmanial activity of the EOs assayed. In addition, SI values of 29.3, 40.1, and 48.9 for C1, C4, and β -caryophyllene (22), respectively, demonstrated a better ratio of efficacy to toxicity. Finally, the C4 sesquiterpene-rich fraction showed a similar antileishmanial activity against amastigote forms, probably due to the same

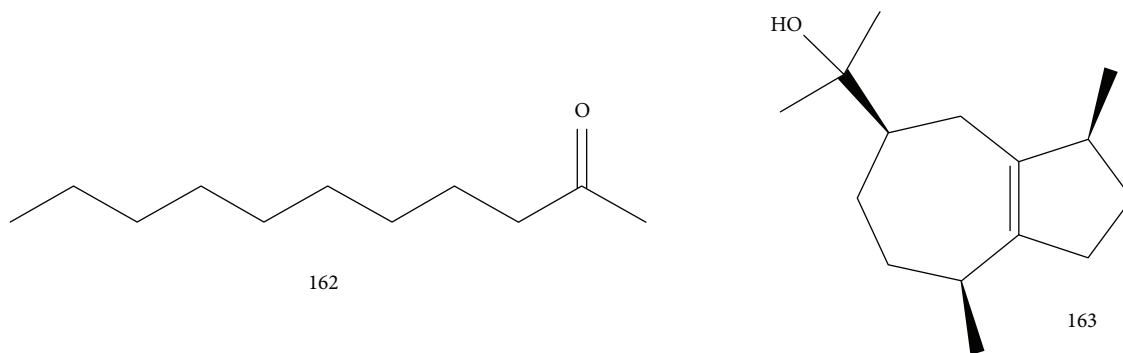


FIGURE 34: Chemical structures of some compounds strongly active (nanomolar concentration) against *Leishmania* species.

concentration of β -caryophyllene (**22**) in both the EO and the fraction, and C4 diterpene-rich fraction was not active in low concentrations [157].

EOs from four plant species reported in traditional medicine in Ethiopia, *Artemisia absinthium* L., *Artemisia abyssinica*, *Echinops kebericho* MESFIN, and *Satureja punctata*, were tested against promastigote and axenic amastigote forms of *L. donovani* and *L. aethiopica*. The results demonstrated that two EOs from *Artemisia absinthium* L. and *Echinops kebericho* MESFIN possessed strong antileishmanicidal activity against promastigote (IC₅₀ ranging from 0.24 to 42.00 $\mu\text{g}/\text{mL}$) and axenic amastigote forms (IC₅₀ ranging from 0.0097 to 0.15 $\mu\text{g}/\text{mL}$) of both *Leishmania* species. In relation to the other two species tested, *Artemisia abyssinica* was inactive against the two forms of parasite, and *Satureja punctata* showed high cytotoxicity. Unfortunately, the great number of constituents (including mono- and sesquiterpenes, aliphatic and aromatic hydrocarbons, carotenoid derivatives, and oxygenated structures) that appeared to have no specific cellular targets could explain the inadequate SI values for the most active oils [158, 159].

In a recent study, Silva and colleagues evaluated the antileishmanial activity of the EO from leaves of *Ocimum canum* Sims. that is commonly used as an infusion or syrup for the treatment of a number of diseases. The biological results revealed that OcEO was rich in monoterpenes such as thymol (**1**) (42.15%), p-cymene (**11**) (21.17%), and γ -terpinene (**64**) (19.81%), demonstrating moderate activity against promastigote and intracellular amastigote forms of *L. amazonensis*, with IC₅₀ values of 17.4 and 13.1 $\mu\text{g}/\text{mL}$, respectively. These values were more potent than those of the reference drug pentamidine, with satisfactory SI values (18.1 and 24.0, respectively) [157]. Electron microscopy showed that OcEO was associated with several ultrastructural alterations in promastigote forms of the parasite, including autophagosome-like structures that were multivesicular and had lipid bodies that could result in cell death, discontinuity of the nucleus membrane, and exocytic activity by the flagellar pocket [160].

EO from leaves and flowers of *Achillea millefolium*, species used as antihelminthic and trypanocidals, was evaluated *in vitro* against *L. amazonensis*. Significant activity was observed against promastigote and intracellular amastigote forms, with IC₅₀ values of 7.8 and 6.5 $\mu\text{g}/\text{mL}$ and acceptable

SI values of 9.2 and 11.0, respectively [161]. Unfortunately, the major constituents of AmEO were not determined. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis of the treated promastigote forms revealed morphological alterations in the shape and size of the parasite as well as ultrastructural alterations, including changes in the flagellar membrane, abnormal membrane structures, rupture of the plasma membrane, atypical vacuoles, myelin-like figures, and vesicles that resembled autophagic vacuoles. The mechanism of action remains unclear; however, the morphological changes observed in the parasite may be related to inhibition of two parasite enzymes: serine-protease and squalene synthase (BPQ-OH) [161].

Rosa et al. investigated the leishmanicidal effects of linalool-rich EO from leaves of *Croton cajucara* and purified linalool (**3**) [162]. Both EO and purified linalool (**3**) showed potent antileishmanial activity, with IC₅₀ values of 8.3 and 4.3 ng/mL against promastigote forms and values of 22.0 and 15.5 ng/mL against the amastigote form of the parasite, respectively. SI values were not determined, but for both, the concentration of 15.0 ng/mL presented no cytotoxic effects against mammalian cells. Mitochondrial swelling and important alterations in the organization of the nuclear and kinetoplast chromatins decrease in the association between macrophages and parasites, and increases in nitric oxide levels in infected macrophages could explain the extreme toxicity of the CcEO for *L. amazonensis* [162].

Some studies reported that linalool (**3**) (oxygenated monoterpene) and eugenol (**2**) (phenolic compound), chemical constituents in many EOs from various plant species, as well as eugenol- and linalool-rich EOs, were fatal for several species of *Leishmania* [162–165]. Dutra and coworkers explored the biological potential of these purified compounds in *L. infantum chagasi* promastigotes and axenic amastigote forms at baseline and during the infection of peritoneal mouse macrophages [166]. The estimated IC₅₀ values for eugenol (**2**) and linalool (**3**) against axenic amastigotes forms were 220 and 550 $\mu\text{g}/\text{mL}$, respectively. The IC₅₀ value for eugenol (**2**) against promastigote forms was 500 $\mu\text{g}/\text{mL}$, and for linalool (**3**), the IC₅₀ value for the last parasite form was not determined. For both compounds, some of the mechanisms associated with leishmanicidal activity were confirmed: the two derivatives were able to enhance the activities of

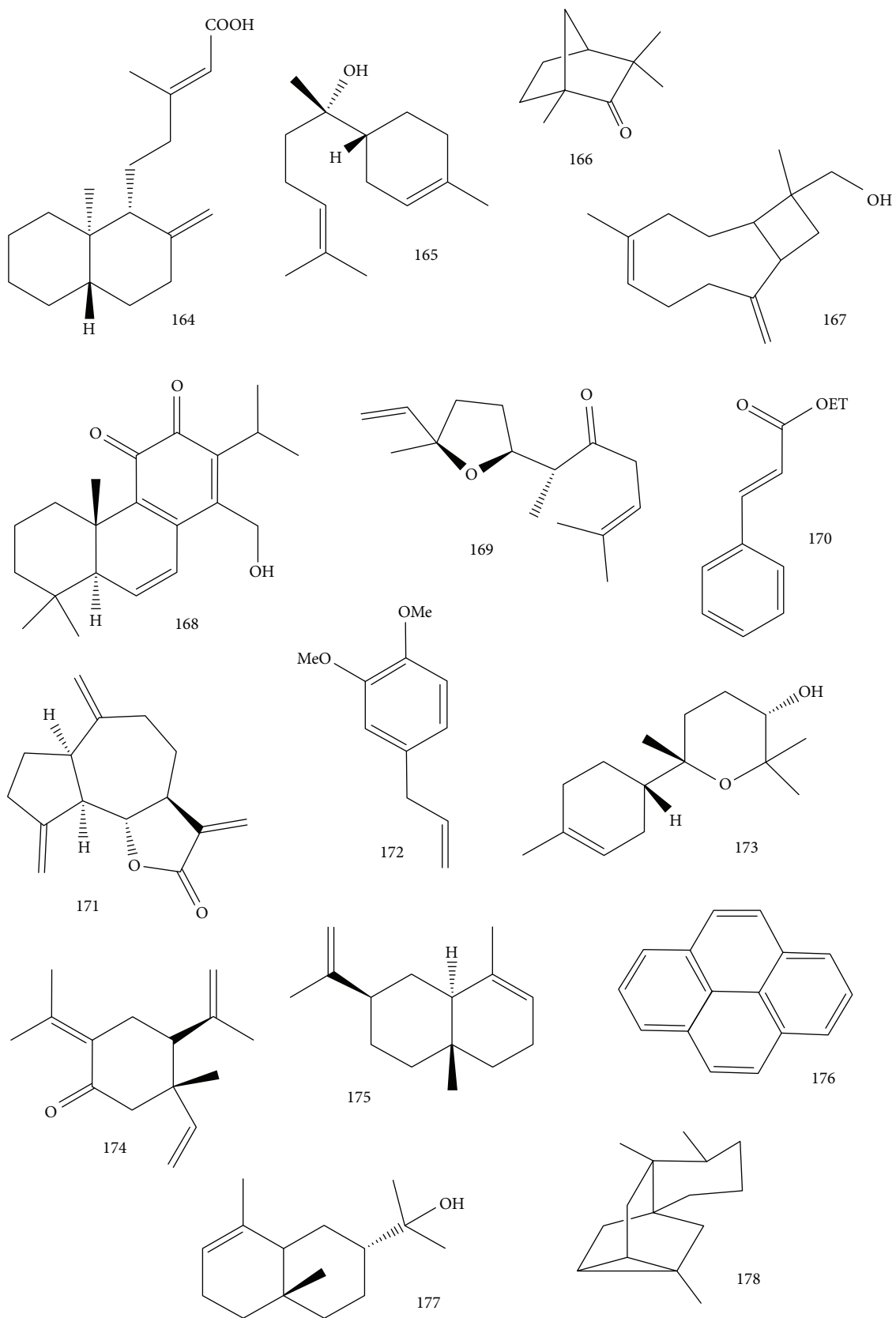


FIGURE 35: Chemical structures of 2-undecanone (**162**) from *Ruta chalepensis* EO and guaiol (**163**) from *Bulnesia sarmientoi* EO actives against *Leishmania* species.

protein kinases PKC and PKA, linalool (**3**) decreased parasite oxygen consumption, and eugenol (**2**) reduced the parasite resistance to reactive oxygen species [166].

Santim et al. (2009) evaluated the effect of EO from *Cymbopogon citratus* and its major constituent, citral (**63**), against *L. amazonensis*. The EO showed good activity against promastigote and amastigote forms, with IC₅₀ values of 1.7 and 3.2 µg/mL, respectively, a good SI value (14.7) for promastigotes and a tolerable value IC₅₀ of 8.7 µg/mL against promastigote forms, with a tolerable SI of 6.3. SEM and TEM analysis revealed aberrant morphologies of the amastigote forms exposed to the EO, including disintegration of the parasite, mitochondrial swelling, exocytic projections in the flagellar pocket, swollen mitochondria, and rupture of the plasma membrane, characterized by the presence of extracellular materials [167].

Rodrigues and colleagues [139, 169] evaluated the antileishmanial potential of EOs from *Eugenia uniflora* L. and *Syzygium cumini* (L.) Skeels, and α -pinene (**118**), major constituents of *EuEO*. α -Pinene (**118**) was more effective than was the EO from the plant, without desirable potency (IC₅₀ \geq 38.1 µg/mL against various forms of the parasite). The isolated compound showed moderate IC₅₀ values (16.1 and 15.6 µg/mL against axenic and intracellular amastigote forms, respectively) and low cytotoxicity (SI > 21.5). The mechanism of action for monoterpene was mediated by immunomodulatory activity (increase in phagocytic and lysosomal activities) and elevated NO levels. However, EO from *E. uniflora* showed significant antileishmanial activity, with IC₅₀ values of 3.04 and 1.92 µg/mL against promastigote and amastigote forms, respectively, and good SI values of 14.9 and 23.9, respectively. In relation to the mechanism of action, this EO activity was not mediated by nitric oxide production, suggesting that macrophage activation may be involved in the biological activity, as demonstrated by increases in both phagocytic capacity and lysosomal activity [168, 169].

Bosquiroli et al. evaluated the antileishmanial activity of EO from *Piper angustifolium*. *PaEO* rich in sesquiterpenes such as spathulenol (**108**) (23.78%) and caryophyllene oxide (**38**) (13.06%) reduced the number of intracellular amastigotes of *L. infantum* with an IC₅₀ value of 1.43 µg/mL. It was more toxic to NIH/3T3 fibroblasts and murine macrophage J774.A1, with good SI values of 33.72 and 22.5, respectively. For *PpEO*, the mechanism of action may be associated with increased NO release after treatment at low concentrations [170].

EOs obtained from the aerial parts of four Moroccan plant species (Lamiaceae) were screened against various *Leishmania* species [171–173]. The EOs from *Lavandula stoechas*, with fenchone (**166**) (31.81%), camphor (**14**) (29.60%), and terpineol (**111**) (13.1%) as major constituents, exhibited strong leishmanicidal effects against two *Leishmania* species, whereas *L. major* was the most sensitive strain with an IC₅₀ of 0.9 µg/mL, followed by *L. infantum* (IC₅₀ = 7.0 µg/mL) and *L. tropica* (IC₅₀ > 10 µg/mL). For the EO from *Origanum compactum*, three phenological stages of the plant were analyzed, and the oxygenated monoterpenes were the major constituents at the three phenological stages (49.4% at vegetative stage, 62.975% at flowering

stage, and 61.379% at postflowering stage). In lower quantities, other chemical classes such as sesquiterpene hydrocarbons, oxygenated sesquiterpenes, alcohols, ketones, and acids were also identified. At low concentrations, these EOs showed significant cytotoxicity against three *Leishmania* species, while the cytotoxic effects are not significantly variable with increasing concentrations. The *L. infantum* species was the most sensitive strain, with IC₅₀ values ranging from 0.02 to 0.12 µg/mL at the three phenological stages. The other two EOs from *Mentha pulegium* and *Rosmarinus o cinalis* were studied by the same authors, and both monoterpene-rich EOs were potent against *L. major*, *L. infantum*, and *L. tropica* species, showing IC₅₀ values ranging from 0.36 to 2.6 µg/mL. Unfortunately, for all EOs studied, the SI values were not determined, and the relationship between efficacy and toxicity could not be measured [171–173].

Essid et al. evaluated the antileishmanial activity of EOs from twelve medicinal plants from Northern Tunisia. The first group of EOs isolated from *Ferula communis*, *Teucrium polium*, and *Pelargonium graveolens* species displayed strong inhibitory activities against the promastigote forms of *L. major* and *L. infantum*, showing IC₅₀ values ranging from 0.05 to 0.28 µg/mL. The second group contained five EOs belonging to *Thymus hirtus*, *Artemisia campestris*, *Myrtus communis*, *Artemisia herba-alba*, and *Alvia o cinalis*, exhibiting good leishmanicidal activities with IC₅₀ values ranging from 1 to 10 µg/mL against the same species of the parasite, but with lower activity when compared with amphotericin B. In the third group, EOs from *Nigella sativa*, *Laurus nobilis*, *Rosmarinus o cinalis*, and *Eucalyptus globulus* showed IC₅₀ values up to 10 µg/mL. Purified β -caryophyllene (**22**), camphor (**14**), and carvacrol (**10**) were screened against the same parasite species and showed less activity when compared with the most active EOs classified as the first group. In addition, the most active EOs and purified compounds showed low cytotoxicity to macrophage cells, presenting ideal values of SI (SI > 10) [174].

An *in vivo* study was performed with the EO extracted from the leaves of *Artemisia annua*, which has camphor (**14**) (52.06%), β -caryophyllene (**22**) (10.95%), and 1,8-cineole (**124**) (5.57%) as major constituents. *AaEO* presented an IC₅₀ value of 7.3 µg/mL against amastigote forms of *L. donovani*, but no cytotoxic effects against mammalian macrophages even at 200 µg/mL. In addition, intraperitoneal administration of the *AaEO* (200 mg/kg/b.w.) to infected BALB/c mice reduced the parasite burden by almost 90% in the liver and spleen, with significant reduction in weight. There was no hepatic or renal toxicity, as demonstrated by normal levels of serum enzymes [163].

Drmachi et al. (2016) evaluated the immunomodulatory effects of EO from *Tetradenia riparia* against *L. amazonensis* species. They found that *TrEO* induced 50% death of amastigote forms of the parasite after 24 h incubation at a concentration of 30 µg/mL. In addition, the oil did not present cytotoxicity in murine macrophages at the same concentration, with cell viability >95%. They evaluated the modulatory effects of *TrEO* on cytokine levels in peritoneal fluid cells that were infected with *L. amazonensis*. They

observed inhibition of some of the most critical cytokines for parasite growth and the establishment of infection, including granulocyte-macrophage colony-stimulating factor, interleukin-4 (IL-4), IL-10, and tumor necrosis factor (TNF). The parasite inhibited interferon- γ and IL-12, and the EO blocked this inhibition, indicating that these cytokines were critical for activating mechanisms associated with the death and elimination of the parasite [175].

EO from *Chenopodium ambrosioides*, containing carvacrol (**10**) (62.36%) and ascaridole (**37**) (22.54%) as major constituents, was investigated against *L. amazonensis*. CaEO showed EC₅₀ values of 3.7 and 4.6 $\mu\text{g}/\text{mL}$ against promastigote and amastigote forms, respectively, and cytotoxicity was approximately 15-fold higher for peritoneal macrophages than for both parasite forms [120]. For the promastigote form, they observed synergistic activity in conjunction with pentamidine [176], and other results showed similar activity against promastigote and amastigote forms of *L. donovani*, with EC₅₀ values of 4.45 and 5.1 $\mu\text{g}/\text{mL}$, respectively [177]. An *in vivo* study demonstrated significant reduction in the size of the lesions in animals treated with the EO during the first 15 days of treatment. They also observed significant suppression of the number of parasites in the infected footpads, as compared with the burden in the footpads of the other treated mice, and oral administration at a dose of 30 mg/kg slowed the infection in an experimental model [178].

In a subsequent study, the authors observed a significant reduction in lesion size in BALB/c mice treated with the EO from *C. ambrosioides* compared with untreated animals at doses of 30 and 150 mg/kg by intralésional and oral routes. This activity was superior to that of the reference drugs glucantime, amphotericin B, and pentamidine, or the two major constituents carvacrol (**10**) and ascaridole (**37**) [179, 180]. This ability to control disease progression of cutaneous leishmaniasis was also observed with EO from *Bixa orellana*, at dose of 30 mg/kg over 14 days [181]. Finally, recent studies suggested that CaEO caused a breakdown of mitochondrial membrane potential and a modification of redox indexes [64], and the isolated compounds carvacrol (**10**), ascaridole (**37**), and caryophyllene oxide (**38**) mediated their leishmanicidal activity via various mitochondrial targets, including the electron transport chain, thiol depletion, and production of superoxide radical, causing significant impairment of mitochondrial coupling [182].

The chemical analysis of EO from *Vanillosmopsis arborea* Baker showed that α -bisabolol (**165**) was its main constituent (97.9%). Both VaEO and α -bisabolol (**165**) efficiently inhibited the growth of *L. amazonensis* promastigotes, with IC₅₀ values of 7.35 and 4.95 $\mu\text{g}/\text{mL}$, respectively [183]. In addition, α -bisabolol (**165**) was more effective against promastigotes and intracellular amastigotes, and the cytotoxic assay against intracellular amastigotes showed that the pure compound (SI = 9.38) was less toxic than was VaEO (SI = 11.52). These results suggested that both α -bisabolol (**165**) and VaEO increased cell permeability to exogenous compounds, since some sesquiterpenes can induce changes in membranes, allowing microorganisms to enter the cells, thus augmenting the microbial permeability to antimicrobial agents.

The ultrastructural analysis of the parasite showed an elongated cell body and the presence of a well-defined kinetoplast and nucleus. The promastigotes treated with α -bisabolol (**165**) for 24 hours at 30 $\mu\text{g}/\text{mL}$ showed severe cell damage with loss of parasite morphology, discontinuity of the nuclear membrane, increased mitochondrial volume and kinetoplast, and presence of vesicles with an electron-dense display with lipid inclusion in the plasma membrane. However, in the same conditions of analysis for VaEO, they observed increased volumes of flagellar pockets with consequent breakage, increased volumes and changes in mitochondrial kinetoplasts, abnormal condensation of chromatin in the nucleus, discontinuity of the nuclear membrane, lipid inclusions in the presence of electron-dense vesicles, and visualization of the inclusion of a lipid envelope within the plasma membrane, with the consequent loss of parasite morphology [183].

Another group evaluated the effect of (-)- α -bisabolol (**165**) against promastigote forms of *L. infantum*. In general, this sesquiterpene showed a very similar percentage of inhibition of the parasite when compared with the reference drug pentamidine (Figure 36). The value of IC₅₀ for the compound was 10.99 $\mu\text{g}/\text{mL}$, and the presence of a hydroxyl in its structure explains its high capacity to inhibit *L. infantum* promastigote form. In addition, the very low toxicity *in vivo* supported the therapeutic use of (-)- α -bisabolol (**165**) to treat leishmaniasis caused by *L. infantum* [184, 185].

Xavier et al. explored the leishmanicidal properties of synthesized compounds derived from the oxygenated monoterpenes eugenol (**2**), thymol (**1**), and carvacrol (**10**), by molecular hybridation with nitrated Morita-Baylis-Hillman adducts (MBHAs) [184]. The general structure and IC₅₀ values of the most potent hybrid compounds against *L. amazonensis* promastigote forms are shown in Figure 37. Hybrid compounds **180**, **181**, and **182** exhibited the best antileishmanial activity, with IC₅₀ values ranging from 4.71 to 8.75 $\mu\text{g}/\text{mL}$, and SI > 45 (except for derivative **3**, which was not determined). In addition, the compounds substituted with nitro groups at the *ortho* position were more bioactive than the *meta* and *para* nitroaryl isomers. Experimental and *in silico* studies indicated that the mechanism of action was connected to nitro group reduction that generated RNO^{-•} [186].

Ten chemical constituents of EOs, including nine monoterpenes and one phenylpropanoid, were investigated as antileishmanial agents against promastigote forms of *L. amazonensis* [187]. Among the monoterpenes evaluated, the positional isomers carvacrol (**10**) and thymol (**1**) that presented a phenolic moiety were the most active compounds, showing moderate antiparasitic activity, with IC₅₀ values of 25.4 and 26.8 $\mu\text{g}/\text{mL}$, respectively. This result suggests that the position of the hydroxyl group in the aromatic ring did not influence the antileishmanial activity. For eugenol (**2**), a hydrogen bond between hydroxyl and *o*-methoxyl groups reduced the release of protons by the OH group, and the acidity of this group may play an important role in the potency of the compounds. In addition, for this series of compounds, the absence of aromatic hydroxyls caused

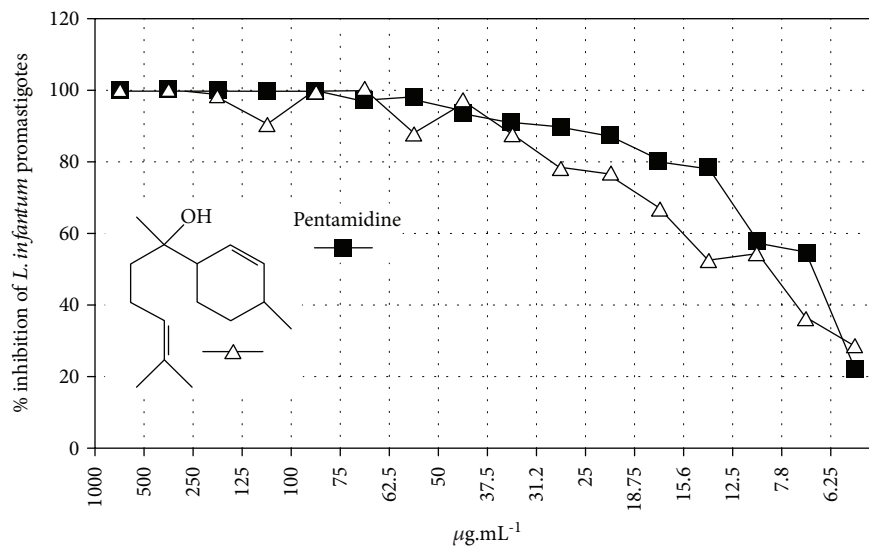


FIGURE 36: Percentage inhibition of *L. infantum* promastigotes for (-)- α -bisabolol (**165**) in comparison with pentamidine.

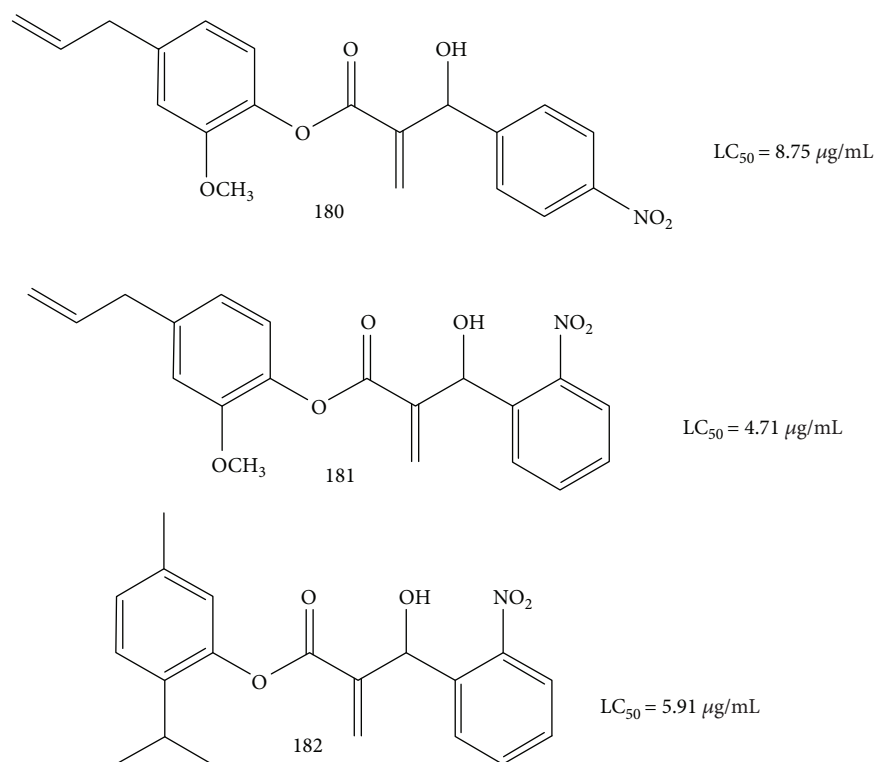


FIGURE 37: MBHA hybrids from eugenol, thymol, and carvacrol, chemical structures and IC_{50} values of the most potent derivatives against of *L. amazonensis* promastigote form.

compounds to be less potent, as observed for *p*-cymene (**11**) and menthol (**130**) with IC_{50} values of up to 198.9 $\mu\text{g/mL}$.

In the same study, the IC_{50} value found for carvacrol (**10**) was different from values reported in the literature for *L. chagasi* and *L. amazonensis* promastigotes ($IC_{50} = 2.3$ [56] and 28.0 [56], and 15.3 $\mu\text{g/mL}$ [188], respectively).

Drug-parasite incubation (24-72 h) and assay methods may explain these differences between values of IC_{50} . For thymol, similar activity was observed by de Medeiros et al., who reported an IC_{50} value of 22.6 $\mu\text{g/mL}$. IC_{50} values ranging from 9.8 to 65.2 $\mu\text{g/mL}$ were found for other species of *Leishmania* [56, 188, 189]. Both eugenol (**2**) and thymol

(1) compounds showed low cytotoxicity at concentrations of 50 and 100 $\mu\text{g}/\text{mL}$, where the percentage of viability on L929 fibroblasts ranged from 46.1 to 64.5%.

1.4. Essentials Oils Active against Arboviruses, Especially Dengue. Arboviruses (arthropod-borne viruses) are viral diseases transmitted to humans by arthropods (insect and arachnid). Among the vectors, one that stands out is the mosquito *Aedes aegypti*, which every year transmits diseases to more than 700 million people worldwide. According to the World Health Organization, it causes more death than any other arboviral disease, killing about 2.5% of all affected children [201].

Aedys aegypti is a carrier of various diseases, including dengue fever, dengue haemorrhagic fever, chikungunya, yellow fever, and even Zika virus [202]. Yellow fever, dengue, and Zika virus have their greatest focus in tropical and subtropical areas [203], while dengue haemorrhagic fever has a greater number of reports in Asia, Thailand, and Indonesia [202].

In recent decades, the spread of dengue has increased worldwide, and in 2012 it was considered the most important viral disease in the world, with more than 100 countries and more than 2.5 billion people (about 40% of the world population) at risk of infection by some mosquito-borne disease. Of this total population, approximately 50-100 million are infected annually, of which 500 thousand cases are considered of greater severity [204, 205]

The mosquito transmits arboviruses through the blood meals of the female. The life cycle consists of egg, larva, pupa, and adult. Eggs are deposited on the walls of any reservoirs containing water, and the ideal temperature range for hatching is 28-33°C; larval and pupal stages take place in the water. The transition phase from larval to pupa lasts 24 hours, and the pupal phase lasts 48 hours until the adult mosquito appears. When adults appear, it takes a few seconds for the stiffening of chitin that allows them to fly [206].

Treatment of dengue, chikungunya, and Zika virus are symptomatic, and vaccines are not yet available. Currently, the only effective way to control these diseases is by breaking the disease transmission cycle, controlling the mosquito population through the use of biological and/or synthetic insecticides and repellents.

In several public health programs, various larvicides and insecticides currently used are effective in eliminating mosquitoes and larvae, including the organophosphates temephos [204] and pyrethroids [207]. However, their continuous use has allowed some mosquitoes to become resistant [204], and the insecticides are not selective, causing damage to other organisms, including humans [205, 208-210]. Temephos, for example, was monitored in 16 countries between 1960 and 2000. It was observed that the agent was active from 48 to 72 hours in water, and it interfered with the viability of other living organisms (in addition to *A. aegypti*), causing serious environmental impact [206].

Currently, in Brazil temephos 1% and Bti (an efficient bioinsecticide) are both used. Bti does not present the same environmental impact as does temephos; however, its high cost makes its general use impossible [206].

In this scenario, it is necessary to identify new larvicides with various modes of action to reduce the development of mechanisms of resistance to pesticides, thereby bolstering public health system efforts [204].

The use of biological agents such as EOs is an alternative to synthetic insecticides, with good selectivity to the target and low toxicity to other organisms and the environment [206, 211, 212].

The use of biological agents has been gaining great prominence, reaching the point of a single review article compiling the larvicidal activity of 361 EOs from 269 plant species. Among these, more than 60% were considered active, with LCs < 100 mg/L [204].

Knowing that it is easier to interfere with the proliferation of *Aedes aegypti* in the larval phase than in the adult phase [208], several EOs are being studied and have already shown to have relevant larvicidal activity, with advantages over synthetic insecticides. Among these advantages, the following stand out: lower risks of allergy, less irritability to the skin, less encephalopathy in children [202], more pleasant odors [201], less toxicity to humans, animals, plant life and other organisms [203], and biodegradable properties [206]. In these terms, EOs are superior for the control of arboviruses [204].

In this context, several authors reported activity of EOs and their phytoconstituents in the control of *Aedes aegypti* adults and larvae. A summary of these studies is presented in Table 3.

Most of the studies, while identifying the constituents of the EO, restricted the experiments of biological activity to the oil itself, with few studies evaluating the activity of each individual substance. In some cases, only the activity of the compounds with the highest concentration was evaluated. This is primarily due to the high cost of these compounds, when they are available for purchase [208].

The monoterpenes were the most tested compounds, especially oxygenated monoterpenes, corresponding to 38% ($n = 49$) of the compounds shown in Table 3. The monoterpene hydrocarbon class presented the best activity. This group included 3-carene (**119**) ($\text{LC}_{50} = 10.7$ and $25.3 \mu\text{g}/\text{mL}$), α -terpinene (**182**) ($\text{LC}_{50} = 14.7 \mu\text{g}/\text{mL}$), and limonene (**8**) ($\text{LC}_{50} = 18.1 \mu\text{g}/\text{mL}$), among others.

Knowing the isolated constituents of the EOs and their activity allowed the execution of chemical analysis and quantitative structure-activity relationship (QSAR), which identifies characteristics related to the structure of the compound that describe the biological activity, making possible the design of new promising compounds.

One study conducted a consensus principal component analysis (CPCA) and principal component analysis (PCA), identifying characteristics related to hydrophobicity (LogS, DRY, and H_2O) of thymol (**1**) and carvacrol (**10**) derivatives that were important to explain the activities of the compounds against larva of *Aedes aegypti* [227]. Another study performed CPCA and PCA in a series of 55 substances isolated from EOs, obtaining similar results. They highlighted the importance of hydrophobicity (DRY and H_2O) for the activity of these compounds against the larva of *Aedes aegypti*; however, steric characteristics were also important to explain this activity, indicating that these characteristics

TABLE 3: Isolated compounds from essential oils and/or synthesized compounds derived from essential oils actives against *Aedes aegypti*.

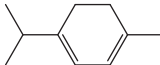
Classes	Chemical Structure of isolated or synthesized compound	LC ₅₀	Reference
Monoterpene hydrocarbons	3-Carene (119)	10.7 µg/mL	[213]
		150 ppm	[214]
		25.3 µg/mL	[215]
	α-Terpinene (183)	14.7 µg/mL	[213]
		14.7 µg/mL	[216]
		28.1 µg/mL	[215]
		37.2 µg/mL	[213]
	γ-Terpinene (64)	30.7 µg/mL	[216]
		26.8 µg/mL	[215]
		56 ppm	[214]
		43.3 µg/mL	[213]
		51 ppm	[217]
	p-Cymene (11)	23.3 ppm	[218]
		19.2 µg/mL	[216]
		37.1 µg/mL	[215]
	β-Pinene (39)	183.8 µg/mL	[213]
	R-Limonene (8)	27 ppm	[214]
		17.8 µL L ⁻¹	[219]
	S-Limonene (8)	30 ppm	[214]
		33.9 ppm	[220]
		13 µL L ⁻¹	[219]
	RS-Limonene (8)	517 ppm	[214]
	18.1 µg/mL	[216]	
β-Myrcene (61)	35.8 µg/mL	[215]	
	120.3 ppm	[221]	
α-Pinene (118)	>50 µg/mL	[216]	
	79.1 µg/mL	[215]	
Terpinolene (141)	28.4 µg/mL	[216]	
	32.1 µg/mL	[215]	
α-Phellandrene (143)	39.3 µg/mL ⁻¹	[222]	
	16.6 µg/mL	[216]	
Camphene (15)	>400 µg/mL	[213]	
(-)-Camphene (15)	220 ppm	[217]	
(+)-Camphene (15)	406 ppm	[217]	
Oxygenated monoterpenes	(-)-α-Terpineol (111)	>400 µg/mL	[213]
		>50 µg/mL	[216]
		>400 µg/mL	[213]
	(-)-Terpinen-4-ol (103)	>50 µg/mL	[216]
		>100 µg/mL	[215]
		81 ppm	[217]
	Thymol (1)	17.5 ppm	[218]
		13.9 ppm	[223]
	Carvacrol (10)	69 ppm	[217]
		20.13 ppm	[223]
Borneol (112)	610 ppm	[217]	
Isoborneol (178)	598 ppm	[217]	
Camphor (14)	657 ppm	[217]	

TABLE 3: Continued.

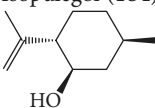
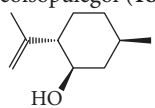
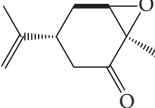
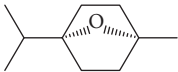

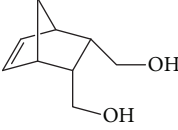
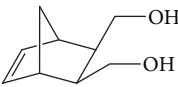
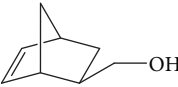
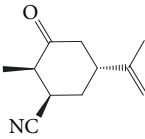
Classes	Chemical Structure of isolated or synthesized compound	LC ₅₀	Reference
	<i>R</i> -Carvone (13)	152 ppm	[217]
	<i>S</i> -Carvone (13)	129.1 ppm	[217]
	<i>RS</i> -Carvone (13)	124 ppm	[217]
	118 ppm	[214]	
	Isopulegol (184)		
		297 ppm	[214]
	Neoisopulegol (185)		
		554 ppm	[214]
	Menthol (130)	404 ppm	[214]
	Menthone (132)	508 ppm	[214]
	1,2-Carvone oxide (186)		
		219 ppm	[214]
	(+)-Pulegone (128)	188.1 ppm	[220]
	1,4-Cineole (187)		
		751 ppm	[217]
	1,8-Cineole (124)	1419 ppm	[217]
		>100 μg/mL ⁻¹	[222]
		>50 μg/mL	[216]
	5-Norbornene-2,2-dimethanol (188)		
		785 ppm	[217]
	5-Norbornene-2-endo,3-endo-dimethanol (189)		
		1407 ppm	[217]
	5-Norbornene-2-exo,3-exo-dimethanol (190)		
		717 ppm	[217]
	5-Norbornene-2-ol (191)		
		759 ppm	[217]
	(1 <i>R</i> ,2 <i>R</i> ,5 <i>R</i>)-2-Methyl-5-(1-methylethenyl)-3-oxo-cyclohex-anecarbonitrile		
		412 ppm	[214]

TABLE 3: Continued.

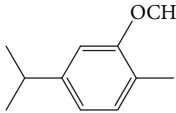
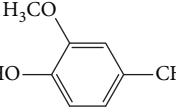
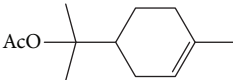
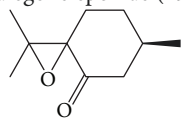
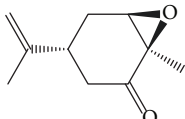
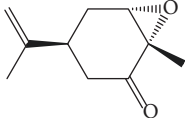
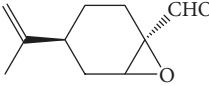
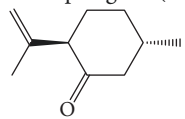
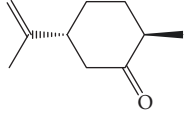
Classes	Chemical Structure of isolated or synthesized compound	LC ₅₀	Reference
	Carvacrol methyl ether (192)		
		40.6 ppm	[223]
	Umbellulone (158)	32.3 ppm	[221]
	Vanillin (193)		
		513 ppm	[217]
	α -Terpinyl acetate (194)		
		>50 μ g/mL	[216]
	Rotundifolone (88)	62.5 ppm	[220]
	Pulegone epoxide (195)		
		1116.2 ppm	[220]
	(-)-Carvone epoxide (196)		
		217.5 ppm	[220]
	(+)-Carvone epoxide (197)		
		254.6 ppm	[220]
	(+)-Limonene epoxide (90)	525.0 ppm	[220]
	(-)-Limonene epoxide (90)	522.5 ppm	[220]
	(-)-Perill aldehyde (92)	115.8 ppm	[220]
	Perillaldehyde epoxide (198)		
		715.1 ppm	[220]
	<i>trans</i> -Isopulegone (199)		
		538.8 ppm	[220]
	<i>trans</i> -dihydrocarvone (200)		
		361.3 ppm	[220]

TABLE 3: Continued.

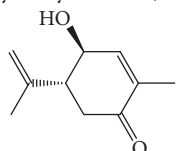
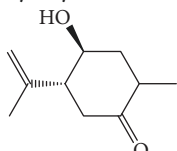
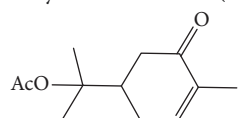
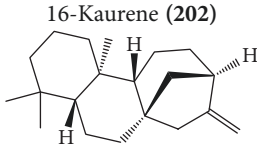
Classes	Chemical Structure of isolated or synthesized compound	LC ₅₀	Reference
	Hydroxycarvone (199) 	1470.9 ppm	[220]
	Hydroxydihydrocarvone (200) 	1628.2 ppm	[220]
	Acetoxycarvotanacetone (201) 	230.7 ppm	[220]
Oxygenated sesquiterpenes	Elemol (52)	>100 µg/mL	[215]
	β-Eudesmol (59)	>50 µg/mL	[224]
		>100 µg/mL	[215]
Diterpenes	16-Kaurene (202) 	57 µg/mL	[213]
		57.0 µg/ml	[217]
Phenylpropanoids	Estragole (74)	46.4 µL L ⁻¹	[219]
		88 ppm	[217]
	Eugenol (2)	93.3 ppm	[224]
		71.9 ppm	[224]
	1-Acetate-2-methoxy-4-(2-propen-1-yl)-phenol	23.4 ppm	[223]
		113.3 ppm	[224]
		107.7 ppm	[224]
	1-Propanoate-2-methoxy-4-(2-propen-1-yl)-phenol	97.2 ppm	[224]
		62.3 ppm	[224]
	1-Benzoate-2-methoxy-4-(2-propen-1-yl)-phenol	706.8 ppm	[224]
		723.2 ppm	[224]

TABLE 3: Continued.

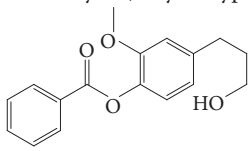
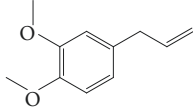
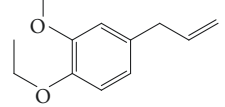
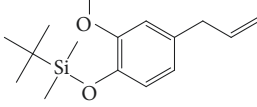
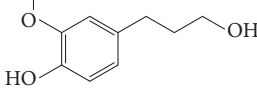
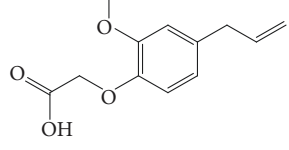
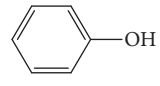
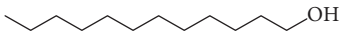
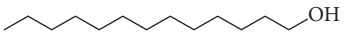
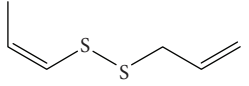
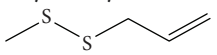
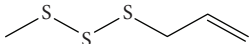
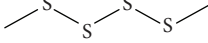
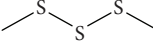
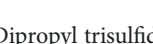
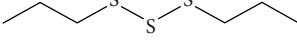

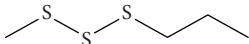
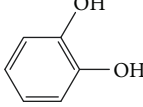
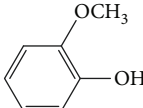
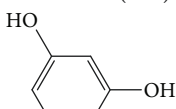
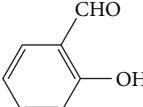
Classes	Chemical Structure of isolated or synthesized compound	LC ₅₀	Reference
	1-Benzoate-2-methoxy-4-(3-hydroxypropyl)-phenol 	166 ppm	[224]
	1,2-Dimethoxy-4-(2-propen-1-yl)-benzene 	107.3 ppm	[224]
	1-Ethoxy-2-methoxy-4-(2-propen-1-yl)-benzene 	67.2 ppm	[224]
	1-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methoxy-4-(2-propen-1-yl)-benzene 	278.9 ppm	[224]
	4-Hydroxy-3-methoxy-benzenepropanol 	1415.1 ppm	[224]
	2-[2-Methoxy-4-(2-propen-1-yl)phenoxy] acetic acid 	295.9 ppm	[224]
	Methyleugenol (171)	36.5 ppm	[221]
	<i>trans</i> -Anethole (153)	29.3 $\mu\text{L L}^{-1}$	[219]
Others	Phenol (203) 	194 ppm	[217]
	1-Dodecanol (204) 	5.2 ppm	[221]
	1-Tridecanol (205) 	2.1 ppm	[221]
	Allyl <i>cis</i> -1-propenyl disulfide 	15.35 ppm	[225]
	Allyl methyl disulfide 	>200 ppm	[225]
			>200 ppm

TABLE 3: Continued.

Classes	Chemical Structure of isolated or synthesized compound	LC ₅₀	Reference
	Allyl methyl trisulfide 	>200 ppm	[225]
	Dimethyl tetrasulfide 	>200 ppm	[226]
	Dimethyl trisulfide 	>200 ppm	[225]
	Dimethyl trisulfide 	>200 ppm	[226]
	Dipropyl trisulfide 	>200 ppm	[225]
	Dipropyl trisulfide 	>200 ppm	[226]
	Methyl propyl trisulfide 	19.38 ppm	[226]
	Catechol (206) 	243 ppm	[217]
	Guaiacol (207) 	177 ppm	[217]
	Resorcinol (208) 	577 ppm	[217]
	Salicylaldehyde (209) 	137 ppm	[217]

were crucial to the activity of these substances, based on the evaluated compounds [228].

2. Conclusions

In this work, a large number of papers that dealt with the use of EOs, their fractions, and/or their chemical constituents as treatment options for some neglected diseases were reviewed. Despite the full knowledge that mankind makes use of plants for medicinal purposes from its origin, the absence of new effective drugs, with fewer side effects that can be used against resistant strains of the parasites, promotes a strong demand for natural products, especially for the poorest and most affected populations that are continuously under risk of these diseases. Several EOs and chemical constituents were identified, which have biological activities

equipotential to those of the few commercial drugs available, with good margins of safety, suggesting that popular use cannot be neglected.

As examples for isolated active compounds against *T. cruzi*, the isolated compounds thymol (**1**) and linalool (**3**) showed similar activity when compared with benznidazole and quantified activity in nanomolar concentrations, respectively. In addition, semisynthetic aphidicolin (**28**) derivatives (diterpenes) exhibited high potency and selectivity against the same parasite.

For EOs with anti-*T. brucei* activity, the isolated compounds rotundifolone (**88**) and (-)-perillyl aldehyde (**92**) were slightly less active than the reference drug suramin, and carvacrol (**10**), ascaridole (**37**), and caryophyllene oxides (**38**) showed strong potential to growth inhibition of the parasite, with activity comparable to the same standard drug. In

addition, some EOs and isolated compounds demonstrated promising antitrypanosomal activity and high selectivity index values, specially the compounds carlina oxide (**139**) (isolated from *Carlina acaulis* roots), linalool (**3**) (which exhibited potential activity against different trypanosome species), and *C. nardus* EO (rich in oxygenated monoterpenes), which demonstrated IC_{50} values ranged from 0.31 to 2.5 $\mu\text{g}/\text{mL}$ and high selectivity index (>40).

For antileishmanial activity, several EOs or isolated compounds were active against the parasite ($IC_{50} \leq 10 \mu\text{g}/\text{mL}$). Some of them promoted morphological alterations in the parasite, but few showed a great ratio of efficacy to toxicity. Linalool-rich EO (from *Croton cajucara*) and purified linalool (**3**) showed potent antileishmanial activity at nanomolar concentration, promoting morphological changes in the parasite, as well as decreased parasite oxygen consumption and enhances the activities of the protein kinases and increases in nitric oxide levels in infected macrophages, confirming some of the mechanisms associated with leishmanicidal activity. Another isolated compound identified as α -bisabolol (**165**) (main constituent of EO from *Vanillosmopsis arborea*) efficiently inhibited the growth of promastigotes and amastigotes forms of the same parasite, inducing several ultrastructural alterations and severe cell damage in the parasite, where the very similar percentage of inhibition (compared with pentamidine) and very low toxicity *in vivo* supported their therapeutic use to treat leishmaniasis.

Other EOs rich in spathulenol (**108**) and caryophyllene oxide (**38**) (from *Piper angustifolium*) and citral (**63**) (from *Cymbopogon citratus*) showed potential activity against promastigote and amastigote forms of the parasite and good SI values.

For control of *Aedes aegypti* adults and larvae, some monoterpene hydrocarbon EOs, specially 3-carene (**119**), α -terpinene (**182**), and limonene (**8**), exhibited the best activity.

In this sense, knowledge of the chemical structures of these phytochemicals may allow them to serve as scaffolds for rational drug design, suggesting chemical modifications to increase activity, bioavailability, and toxicity, among other characteristics, allowing the design of new and more active compounds.

Conflicts of Interest

The authors declare no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors acknowledge the financial support from the Brazilian agency CNPq and from State University of Paraiba (UEPB). F.J.B.M.J. is granted by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) PQ #308590/2017-1. E.C.L. and R.S.A.A. are granted by FAPESQ-CNPQ (fellowships).

Supplementary Materials

Figure S1: plant families and number of OEs evaluated between the years 2000 and 2018 against at least one species of *Leishmania*. Figure S2: plant families and the number of active EOs ($IC_{50} \leq 10 \mu\text{g}/\text{mL}$) against at least one *Leishmania* species and parasite form. Table S1: inactive or moderated active EOs against *Leishmania* species. (*Supplementary Materials*)

References

- [1] WHO/Department of control of neglected tropical diseases, *Sustaining the Drive to Overcome the Global Impact of Neglected Tropical Diseases: Second WHO Report on Neglected Diseases*, WHO, Geneva, Switzerland, 2012.
- [2] WHO, *First Who Report Neglected Tropical Diseases: Working to Overcome the Global Impact Neglected Tropical Diseases*, WHO/HTMA/NTD/2010, Geneva, Switzerland, 2018, http://www.who.int/neglected_diseases/2010report/en/.
- [3] F. J. B. Mendonça Junior, "Chapter 1: "As doenças negligenciadas e seu contexto no Brasil", in *Doenças Negligenciadas Sob a ótica da Química Medicinal*, pp. 11–26, CRV, Curitiba-Parana, Brazil, 1st edition edition, 2015.
- [4] M. C. Yazbek, "Pobreza no Brasil contemporâneo e formas de seu enfrentamento," *Serviço Social & Sociedade*, vol. 110, no. 110, pp. 288–322, 2012.
- [5] S. S. d. Assis and T. C. Araujo-Jorge, "O que dizem as propostas curriculares do Brasil sobre o tema saúde e as doenças negligenciadas?: aportes para a educação em saúde no ensino de ciências," *Ciência & Educação*, vol. 24, no. 1, pp. 125–140, 2018.
- [6] B. Nikolay, C. S. Mwandawiro, J. H. Kihara et al., "Understanding heterogeneity in the impact of national neglected tropical disease control programmes: evidence from school-based deworming in Kenya," *PLOS Neglected Tropical Diseases*, vol. 9, no. 9, article e0004108, 2015.
- [7] P. J. Hotez, "The giant anteater in the room: Brazil's neglected tropical diseases problem," *PLoS Neglected Tropical Diseases*, vol. 2, no. 1, p. e177, 2008.
- [8] R. Siqueira-Batista and F. R. Schramm, "A saúde entre a iniquidade e a justiça: contribuições da igualdade complexa de Amartya Sen," *Ciência & Saúde Coletiva*, vol. 10, no. 1, pp. 129–142, 2005.
- [9] B. L. A. d. ANDRADE and D. G. ROCHA, "Há equidade na produção do conhecimento sobre as doenças negligenciadas no Brasil?," *Tempus Actas de Saúde Coletiva*, vol. 9, no. 3, pp. 21–34, 2015.
- [10] V. I. Avelino-Silva and J. F. Ramos, "Arboviroses e políticas públicas no Brasil/Arboviruses and public policies in Brazil," *Revista Ciências Em Saúde*, vol. 7, no. 3, p. 1, 2017.
- [11] L. C. Almeida Filho, P. M. Tabosa, D. C. Hissa, I. M. Vasconcelos, and A. F. Carvalho, "First insights into insecticidal activity against *Aedes aegypti* and partial biochemical characterization of a novel low molecular mass chymotrypsin-trypsin inhibitor purified from *Lonchocarpus sericeus* seeds," *Pest Management Science*, vol. 74, no. 6, pp. 1362–1373, 2018.
- [12] I. R. Barbosa, A. M. Tavares, Ú. P. S. Torres et al., "Identificação de áreas prioritárias para a vigilância e controle de dengue e outras arboviroses transmitidas pelo *Aedes aegypti* no

- município de Natal-RN: relato de experiência,” *Epidemiologia e Serviços de Saúde*, vol. 26, no. 3, pp. 629–638, 2017.
- [13] K. M. Arantes and B. B. Pereira, “Levantamento, análise e seleção de indicadores ambientais e socioeconômicos como subsídio para o fortalecimento das estratégias de controle da dengue no município de Uberlândia-MG,” *Journal of Health & Biological Sciences*, vol. 5, no. 1, pp. 86–95, 2017.
- [14] T. Honorato, P. P. A. Lapa, C. M. M. Sales et al., “Spatial analysis of distribution of dengue cases in Espírito Santo, Brazil, in 2010: use of Bayesian model,” *Revista Brasileira de Epidemiologia*, vol. 17, Supplement 2, pp. 150–159, 2014.
- [15] C. A. S. F. Miranda, M. d. G. Cardoso, L. R. Batista, L. M. A. Rodrigues, and A. C. d. S. Figueiredo, “Essential oils from leaves of various species: antioxidant and antibacterial properties on growth in pathogenic species,” *Revista Ciência Agronômica*, vol. 47, no. 1, pp. 213–220, 2016.
- [16] L. Scotti, F. J. B. Mendonça Júnior, M. S. Silva, and M. T. Scotti, “4. Drug design applied to natural products against neglected diseases,” in *Chemical Drug Design*, G. K. Gupta and V. Kumar, Eds., pp. 53–86, De Gruyter, Berlin, Boston, 2016.
- [17] P. L. Crowell, “Prevention and therapy of cancer by dietary monoterpenes,” *The Journal of Nutrition*, vol. 129, no. 3, pp. 775S–778S, 1999.
- [18] S. L. N. Kamte, F. Ranjbarian, G. D. Campagnaro et al., “Trypanosoma brucei inhibition by essential oils from medicinal and aromatic plants traditionally used in Cameroon (Azadirachta indica, Aframomum melegueta, Aframomum daniellii, Clausena anisata, Dichrostachys cinerea and Echinops giganteus),” *International Journal of Environmental Research and Public Health*, vol. 14, no. 7, p. 737, 2017.
- [19] C. M. O. Simões, E. P. Schenkel, G. Gosmann, J. C. P. Mello, L. A. Mentz, and P. R. Petrovick, “Farmacognosia da planta ao medicamento,” Porto Alegre: Editora da UFRGS and UFSC, Florianópolis, 6th edition, 2010.
- [20] A. A. Craveiro and M. I. L. D. Machado, “Aromas, insetos e plantas,” *Ciência Hoje*, vol. 4, no. 23, pp. 54–63, 1986.
- [21] G. Benelli, “Research in mosquito control: current challenges for a brighter future,” *Parasitology Research*, vol. 114, no. 8, pp. 2801–2805, 2015.
- [22] G. Benelli and H. Mehlhorn, “Declining malaria, rising of dengue and Zika virus: insights for mosquito vector control,” *Parasitology Research*, vol. 115, no. 5, pp. 1747–1754, 2016.
- [23] A. Silva-Santos, H. R. Bizzo, A. M. Antunes, and I. A. D’ávila, “A proteção patentária na utilização de óleos essenciais e compostos terpenicos para o desenvolvimento tecnológico e industrial,” *Revista Brasileira de Plantas Mediciniais*, vol. 8, no. 4, pp. 14–22, 2006.
- [24] C. M. d. M. Sousa, H. R. e. Silva, G. M. Vieira-Jr et al., “Fenóis totais e atividade antioxidante de cinco plantas medicinais,” *Química Nova*, vol. 30, no. 2, pp. 351–355, 2007.
- [25] F. Solórzano-Santos and M. G. Miranda-Novales, “Essential oils from aromatic herbs as antimicrobial agents,” *Current Opinion in Biotechnology*, vol. 23, no. 2, pp. 136–141, 2012.
- [26] M. Fazolin, J. L. V. Estrela, V. Catani, M. R. Alécio, and M. S. Lima, “Propriedade inseticida dos óleos essenciais de *Piper hispidinervum* C. DC.; *Piper aduncum* L. e *Tanaecium nocturnum* (Barb. Rodr.) Bur. & K. Shum sobre *Tenebrio molitor* L., 1758,” *Ciência e Agrotecnologia*, vol. 31, no. 1, pp. 113–120, 2007.
- [27] A. C. R. L. Pereira, J. V. d. Oliveira, M. G. C. Gondim Junior, and C. A. G. d. Câmara, “Atividade inseticida de óleos essenciais e fixos sobre *Callosobruchus maculatus* (FABR., 1775) (Coleoptera: Bruchidae) em grãos de caupi [*Vigna unguiculata* (L.) WALP.]” *Ciência e Agrotecnologia*, vol. 32, no. 3, pp. 717–724, 2008.
- [28] A. C. T. d. Campos, L. L. Radunz, A. L. Radünz, A. J. Mossi, R. G. Dionello, and S. L. Ecker, “Atividade repelente e inseticida do óleo essencial de carqueja doce sobre o caruncho do feijão,” *Revista Brasileira de Engenharia Agrícola e Ambiental*, vol. 18, no. 8, pp. 861–865, 2014.
- [29] P. J. C. Sousa, C. A. L. Barros, J. C. S. Rocha, D. S. Lira, G. M. Monteiro, and J. G. S. Maia, “Avaliação toxicológica do óleo essencial de *Piper aduncum* L.,” *Revista Brasileira de Farmacognosia*, vol. 18, no. 2, pp. 217–221, 2008.
- [30] G. L. P. Gonçalves, L. P. Ribeiro, L. Gimenes et al., “Lethal and sublethal toxicities of *Annona sylvatica* (Magnoliales: Annonaceae) extracts to *Zabrotes subfasciatus* (Coleoptera: Chrysomelidae: Bruchinae),” *Florida Entomologist*, vol. 98, no. 3, pp. 921–928, 2015.
- [31] T. I. d. Silva, A. C. L. Alves, F. R. Azevedo, C. A. Marco, H. R. Santos, and W. S. Alves, “Efeito larvicida de óleos essenciais de plantas medicinais sobre larvas de *Aedes aegypti* L. (Diptera: Culicidae),” *Revista Verde de Agroecologia e Desenvolvimento Sustentável*, vol. 12, no. 2, pp. 256–261, 2017.
- [32] C. S. Teixeira, C. C. Nunes, R. Vargas, J. R. de Carvalho, and H. B. Zago, “Toxicidade de óleos essenciais para o controle de *Tetranychus urticae* KOCH, 1836 (Acari: tetranychidae),” *Revista Univap*, vol. 22, no. 40, pp. 843–843, 2016.
- [33] A. L. de Sene Amâncio Zara, S. M. dos Santos, E. S. Fernandes-Oliveira, R. G. Carvalho, and G. E. Coelho, “Estratégias de controle do *Aedes aegypti*: uma revisão,” *Epidemiologia e Serviços de Saúde*, vol. 25, no. 2, pp. 1–2, 2016.
- [34] D. G. d. R. Voris, C. H. V. Afonso, C. A. C. A. Filho et al., “Estudos Etnofarmacológicos de óleos essenciais com atividade larvicida contra o Mosquito *Aedes Aegypt*,” *Semioses*, vol. 11, no. 1, pp. 86–94, 2017.
- [35] R. Torres-Martínez, Y. M. García-Rodríguez, P. Ríos-Chávez et al., “Antioxidant activity of the essential oil and its major terpenes of *Satureja macrostema* (Moc. and Sessé ex Benth.) Briq,” *Pharmacognosy Magazine*, vol. 13, Supplement 4, pp. S875–S880, 2018.
- [36] E. González-Burgos and M. P. Gómez-Serranillos, “Terpene compounds in nature: a review of their potential antioxidant activity,” *Current Medicinal Chemistry*, vol. 19, no. 31, pp. 5319–5341, 2012.
- [37] A. Khan, A. Ahmad, F. Akhtar et al., “Induction of oxidative stress as a possible mechanism of the antifungal action of three phenylpropanoids,” *FEMS Yeast Research*, vol. 11, no. 1, pp. 114–122, 2011.
- [38] H. S. Camargos, R. A. Moreira, S. A. Mendanha, K. S. Fernandes, M. L. Dorta, and A. Alonso, “Terpenes increase the lipid dynamics in the *Leishmania* plasma membrane at concentrations similar to their IC₅₀ values,” *PLoS One*, vol. 9, no. 8, article e104429, 2014.
- [39] S. A. Mendanha and A. Alonso, “Effects of terpenes on fluidity and lipid extraction in phospholipid membranes,” *Biophysical Chemistry*, vol. 198, pp. 45–54, 2015.
- [40] J. Bero, S. Kpoviessi, and J. Quetin-Leclercq, “Anti-parasitic activity of essential oils and their active constituents against *Plasmodium*, *Trypanosoma* and *Leishmania*,” in *Novel Plant*

- Bioresources: Applications in Food, Medicine and Cosmetics*, A. Gurib-Fakim, Ed., John Wiley & Sons, Ltd., 2014.
- [41] J. A. Pérez-Molina and I. Molina, "Chagas disease," *The Lancet*, vol. 391, no. 10115, pp. 82–94, 2018.
- [42] World Health Organization, "Investing to overcome the global impact of neglected tropical diseases," *WHO Third Report on Neglected Tropical Diseases 2015* WHO, Geneva, Switzerland May 2018, http://apps.who.int/iris/bitstream/10665/152781/1/9789241564861_eng.pdf.
- [43] G. Zanusso Junior, M. Massago, D. Kian, and M. J. O. Toledo, "Efficacy of essential oil of *Syzygium aromaticum* alone and in combination with benzimidazole on murine oral infection with *Trypanosoma cruzi* IV," *Experimental Parasitology*, vol. 185, pp. 92–97, 2018.
- [44] S. R. Johann, R. U. Joahan, B. Ríos et al., "Actividad antiparasitaria de plantas medicinales de la Amazonía Peruana," *Biofarbo*, vol. 17, no. 2, pp. 23–33, 2009.
- [45] E. Izumi, T. Ueda-Nakamura, V. F. Veiga Jr, A. C. Pinto, and C. V. Nakamura, "Terpenes from *Copaifera* demonstrated in vitro antiparasitic and synergic activity," *Journal of Medicinal Chemistry*, vol. 55, no. 7, pp. 2994–3001, 2012.
- [46] D. S. Alviano, A. L. S. Barreto, F. A. Dias et al., "Conventional therapy and promising plant-derived compounds against trypanosomatid parasites," *Frontiers in Microbiology*, vol. 3, no. 3, pp. 283–293, 2012.
- [47] F. Bakkali, S. Averbeck, D. Averbeck, and M. Idaomar, "Biological effects of essential oils – a review," *Food and Chemical Toxicology*, vol. 46, no. 2, pp. 446–475, 2008.
- [48] J. Cardoso and M. J. Soares, "In vitro effects of citral on *Trypanosoma cruzi* metacyclogenesis," *Memórias do Instituto Oswaldo Cruz*, vol. 105, no. 8, pp. 1026–1032, 2010.
- [49] M. d. G. F. de Medeiros, A. C. da Silva, A. M. d. G. L. Citó et al., "In vitro antileishmanial activity and cytotoxicity of essential oil from *Lippia sidoides* Cham," *Parasitology International*, vol. 60, no. 3, pp. 237–241, 2011.
- [50] A. O. dos Santos, T. Ueda-Nakamura, B. P. Dias Filho, V. F. da Veiga Junior, and C. V. Nakamura, "Copaiba oil: an alternative to development of new drugs against Leishmaniasis," *Evidence-based Complementary and Alternative Medicine*, vol. 2012, Article ID 898419, 7 pages, 2012.
- [51] F. B. Holetz, T. Ueda-Nakamura, B. P. Dias-Filho, D. A. G. Cortez, J. C. P. Mello, and C. V. Nakamura, "Effect of plant extracts used in folk medicine on cell growth and differentiation of *Herpetomonas samuelpessoai* (Kinetoplastida, Trypanosomatidae) cultivated in defined medium," *Acta Scientiarum*, vol. 24, no. 3, pp. 657–662, 2002.
- [52] F. B. Holetz, T. Ueda-Nakamura, B. P. Filho, D. A. Cortez, J. A. Morgado-Diaz, and C. V. Nakamura, "Effect of essential oil of *Ocimum gratissimum* on the Trypanosomatid *Herpetomonas samuelpessoai*," *Acta Protozoologica*, vol. 42, pp. 269–276, 2003.
- [53] G. F. Santoro, M. das Graças Cardoso, L. G. L. Guimarães, A. P. S. P. Salgado, R. F. S. Menna-Barreto, and M. J. Soares, "Effect of oregano (*Origanum vulgare* L.) and thyme (*Thymus vulgaris* L.) essential oils on *Trypanosoma cruzi* (Protozoa: Kinetoplastida) growth and ultrastructure," *Parasitology Research*, vol. 100, no. 4, pp. 783–790, 2007.
- [54] G. F. Santoro, M. G. Cardoso, L. G. L. Guimarães, L. Z. Mendonça, and M. J. Soares, "*Trypanosoma cruzi*: activity of essential oils from *Achillea millefolium* L., *Syzygium aromaticum* L. and *Ocimum basilicum* L. on epimastigotes and trypomastigotes," *Experimental Parasitology*, vol. 116, no. 3, pp. 283–290, 2007.
- [55] R. F. S. Menna-Barreto, G. A. T. Laranja, M. C. C. Silva et al., "Anti-*Trypanosoma cruzi* activity of *Pterodon pubescens* seed oil: geranylgeraniol as the major bioactive component," *Parasitology Research*, vol. 103, no. 1, pp. 111–117, 2008.
- [56] P. Escobar, S. Milena Leal, L. V. Herrera, J. R. Martinez, and E. Stashenko, "Chemical composition and antiprotozoal activities of Colombian *Lippia* spp essential oils and their major components," *Memórias do Instituto Oswaldo Cruz*, vol. 105, no. 2, pp. 184–190, 2010.
- [57] J. Rojas, H. Solís, and O. Palacios, "Evaluación in vitro de la actividad anti *Trypanosoma cruzi* de aceites esenciales de diez plantas medicinales," *Anales de la Facultad de Medicina*, vol. 71, no. 3, p. 161, 2011.
- [58] J. Rojas, S. Ronceros, O. Palacios, and C. Sevilla, "Efecto anti-*Trypanosoma cruzi* del aceite esencial de *Cymbopogon citratus* (DC) Stapf (hierba luisa) en ratones Balb/c," *Anales de la Facultad de Medicina*, vol. 73, no. 1, p. 7, 2012.
- [59] J. Rojas, O. Palacios, and S. Ronceros, "Efecto del aceite esencial de *aloesia triphylla* britton (cedrón) sobre el *Trypanosoma cruzi* en ratones," *Revista Peruana de Medicina Experimental y Salud Pública*, vol. 29, no. 1, pp. 61–68, 2012.
- [60] T. G. Santos, R. A. Rebelo, E. M. Dalmarco et al., "Composição química e avaliação da atividade antimicrobiana do óleo essencial das folhas de *Piper malacophyllum* (C. PRESL.) C. DC," *Química Nova*, vol. 35, no. 3, pp. 477–481, 2012.
- [61] A. R. Borges, J. R. A. Aires, T. M. M. Higino et al., "Trypanocidal and cytotoxic activities of essential oils from medicinal plants of Northeast of Brazil," *Experimental Parasitology*, vol. 132, no. 2, pp. 123–128, 2012.
- [62] V. Esperandim, D. da Silva Ferreira, K. Sousa Rezende et al., "In vitro antiparasitic activity and chemical composition of the essential oil obtained from the fruits of *Piper cubeba*," *Planta Medica*, vol. 79, no. 17, pp. 1653–1655, 2013.
- [63] C. M. O. Azeredo, T. G. Santos, B. H. L. N. S. Maia, and M. J. Soares, "In vitro biological evaluation of eight different essential oils against *Trypanosoma cruzi*, with emphasis on *Cinnamomum verum* essential oil," *BMC Complementary and Alternative Medicine*, vol. 14, no. 1, 2014.
- [64] L. Monzote, M. García, J. Pastor et al., "Essential oil from *Chenopodium ambrosioides* and main components: activity against *Leishmania*, their mitochondria and other microorganisms," *Experimental Parasitology*, vol. 136, pp. 20–26, 2014.
- [65] M. A. Andrade, M. G. Cardoso, M. S. Gomes et al., "Biological activity of the essential oils from *Cinnamodendron dinisii* and *Siparuna guianensis*," *Brazilian Journal of Microbiology*, vol. 46, no. 1, pp. 189–194, 2015.
- [66] E. Guenther, *Individual Essential Oils of the Plant Families Rutaceae and Labiatae*, E. Robert, Ed., vol. 3, Krieger Publishing Company, Inc., New York, NY, USA, 1975.
- [67] L. Barros, A. Duarte, M. Morais-Braga et al., "Chemical characterization and trypanocidal, leishmanicidal and cytotoxicity potential of *Lantana camara* L. (Verbenaceae) essential oil," *Molecules*, vol. 21, no. 2, pp. 209–218, 2016.
- [68] M. V. O. Barros de Alencar, J. M. de Castro e Sousa, H. M. L. Rolim et al., "Diterpenes as lead molecules against neglected tropical diseases," *Phytotherapy Research*, vol. 31, no. 2, pp. 175–201, 2017.

- [69] G. B. Santos, R. Krogh, L. G. Magalhaes, A. D. Andricopulo, M. T. Pupo, and F. S. Emery, "Semisynthesis of new Aphidicolin derivatives with high activity against *Trypanosoma cruzi*," *Bioorganic & Medicinal Chemistry Letters*, vol. 26, no. 4, pp. 1205–1208, 2016.
- [70] M. T. Varela, R. Z. Dias, L. F. Martins et al., "Gibbilibol analogues as antiparasitic agents — synthesis and biological activity against *Trypanosoma cruzi* and *Leishmania* (L.) *infantum*," *Bioorganic & Medicinal Chemistry Letters*, vol. 26, no. 4, pp. 1180–1183, 2016.
- [71] M. T. Varela, M. L. Lima, M. K. Galuppo et al., "New alkenyl derivative from Piper malacophyllum and analogues: anti-parasitic activity against *Trypanosoma cruzi* and *Leishmania infantum*," *Chemical Biology & Drug Design*, vol. 90, no. 5, pp. 1007–1011, 2017.
- [72] L. I. Oliveira de Souza, P. C. Bezzerá-Silva, D. M. do Amaral Ferraz Navarro et al., "The chemical composition and trypanocidal activity of volatile oils from Brazilian Caatinga plants," *Biomedicine & Pharmacotherapy*, vol. 96, pp. 1055–1064, 2017.
- [73] L. H. Villamizar, M. G. Cardoso, J. Andrade et al., "Linalool, a Piper aduncum essential oil component, has selective activity against *Trypanosoma cruzi* trypomastigote forms at 4°C," *Memórias do Instituto Oswaldo Cruz*, vol. 112, no. 2, pp. 131–139, 2017.
- [74] D. Steverding, "The development of drugs for treatment of sleeping sickness: a historical review," *Parasites & Vectors*, vol. 3, no. 1, p. 15, 2010.
- [75] World Health Organization (WHO), "World Health Statistic," 2011, <http://www.who.int/whosis/whostat/2011/en/index.html>.
- [76] J. E. Donelson, "Antigenic variation and the African trypanosome genome," *Acta Tropica*, vol. 85, no. 3, pp. 391–404, 2003.
- [77] P. Cattand, J. Jannin, and P. Lucas, "Sleeping sickness surveillance: an essential step towards elimination," *Tropical Medicine & International Health*, vol. 6, no. 5, pp. 348–361, 2001.
- [78] World Health Organization (WHO), "African trypanosomiasis (sleeping sickness)," 2012, <http://www.who.int/mediacentre/factsheets/fs259/en/>.
- [79] D. Malvy and F. Chappuis, "Sleeping sickness," *Clinical Microbiology and Infection*, vol. 17, no. 7, pp. 986–995, 2011.
- [80] P. Holmes, "Tsetse-transmitted trypanosomes – their biology, disease impact and control," *Journal of Invertebrate Pathology*, vol. 112, Supplement 1, pp. S11–S14, 2013.
- [81] R. Petrelli, F. Ranjbarian, S. Dall'Acqua et al., "An overlooked horticultural crop, *Smyrniololus olusatrum*, as a potential source of compounds effective against African trypanosomiasis," *Parasitology International*, vol. 66, no. 2, pp. 146–151, 2017.
- [82] S. Gehrig and T. Efferth, "Development of drug resistance in *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. Treatment of human African trypanosomiasis with natural products (review)," *International Journal of Molecular Medicine*, vol. 22, no. 4, pp. 411–419, 2008.
- [83] F. Astelbauer and J. Walochnik, "Antiprotozoal compounds: state of the art and new developments," *International Journal of Antimicrobial Agents*, vol. 38, no. 2, pp. 118–124, 2011.
- [84] R. Brun, J. Blum, F. Chappuis, and C. Burri, "Human African trypanosomiasis," *Lancet*, vol. 375, no. 9709, pp. 148–159, 2010.
- [85] World Health Organization (WHO), *Control and Surveillance of Human African Trypanosomiasis*, vol. 984, World Health Organisation Technical Report Series, 2013.
- [86] P. G. E. Kennedy, "The continuing problem of human African trypanosomiasis (sleeping sickness)," *Annals of Neurology*, vol. 64, no. 2, pp. 116–126, 2008.
- [87] P. G. E. Kennedy, "Human African trypanosomiasis of the CNS: current issues and challenges," *The Journal of Clinical Investigation*, vol. 113, no. 4, pp. 496–504, 2004.
- [88] S. Costa, C. Cavadas, C. Cavaleiro, L. Salgueiro, and M. do Céu Sousa, "In vitro susceptibility of *Trypanosoma brucei brucei* to selected essential oils and their major components," *Experimental Parasitology*, vol. 190, pp. 34–40, 2018.
- [89] S. L. Croft, S. Sundar, and A. H. Fairlamb, "Drug resistance in leishmaniasis," *Clinical Microbiology Reviews*, vol. 19, no. 1, pp. 111–126, 2006.
- [90] Ashutosh, S. Sundar, and N. Goyal, "Molecular mechanisms of antimony resistance in *Leishmania*," *Journal of Medical Microbiology*, vol. 56, no. 2, Part 2, pp. 143–153, 2007.
- [91] T. V. Piscopo and A. C. Mallia, "Leishmaniasis," *Postgraduate Medical Journal*, vol. 82, no. 972, pp. 649–657, 2006.
- [92] S. Hoet, F. Opperdoes, R. Brun, and J. Quetin-Leclercq, "Natural products active against African trypanosomes: a step towards new drugs," *Natural Product Reports*, vol. 21, no. 3, pp. 353–364, 2004.
- [93] F. Herrmann, F. Sporer, A. Tahrani, and M. Wink, "Antitrypanosomal properties of *Panax ginseng* C. A. Meyer: new possibilities for a remarkable traditional drug," *Phytotherapy Research*, vol. 27, no. 1, pp. 86–98, 2013.
- [94] E. Nibret and M. Wink, "Trypanocidal and antileukaemic effects of the essential oils of *Hagenia abyssinica*, *Leonotis ocyimifolia*, *Moringa stenopetala*, and their main individual constituents," *Phytomedicine*, vol. 17, no. 12, pp. 911–920, 2010.
- [95] A. H. Fairlamb, "Chemotherapy of human African trypanosomiasis: current and future prospects," *Trends in Parasitology*, vol. 19, no. 11, pp. 488–494, 2003.
- [96] S. L. Croft, "The current status of antiparasite chemotherapy," *Parasitology*, vol. 114, pp. S3–S15, 1997.
- [97] G. Hide, J. C. Mottram, G. H. Coombs, and P. H. Holmes, *Trypanosomiasis and Leishmaniasis: Biology and Control*, CAB International, Wallingford-UK, 1997.
- [98] A. J. Jones and V. M. Avery, "Future treatment options for human African trypanosomiasis," *Expert Review of Anti-Infective Therapy*, vol. 13, no. 12, pp. 1429–1432, 2015.
- [99] G. Benelli, "Gold nanoparticles – against parasites and insect vectors," *Acta Tropica*, vol. 178, pp. 73–80, 2018.
- [100] S. Hoet, F. Opperdoes, R. Brun, V. Adjakidjé, and J. Quetin-Leclercq, "In vitro antitrypanosomal activity of ethnopharmacologically selected Beninese plants," *Journal of Ethnopharmacology*, vol. 91, no. 1, pp. 37–42, 2004.
- [101] J. Bero, V. Hannaert, G. Chataigné, M. F. Hérent, and J. Quetin-Leclercq, "In vitro antitrypanosomal and antileishmanial activity of plants used in Benin in traditional medicine and bio-guided fractionation of the most active extract," *Journal of Ethnopharmacology*, vol. 137, no. 2, pp. 998–1002, 2011.

- [102] S. Geerts, P. H. Holmes, M. C. Eisler, and O. Dially, "African bovine trypanosomiasis: the problem of drug resistance," *Trends in Parasitology*, vol. 17, no. 1, pp. 25–28, 2001.
- [103] S. Hoet, C. Stévigny, S. Block et al., "Alkaloids from *Cassytha filiformis* and related aporphines: antitrypanosomal activity, cytotoxicity, and interaction with DNA and topoisomerases," *Planta Medica*, vol. 70, no. 5, pp. 407–413, 2004.
- [104] D. J. Newman, G. M. Cragg, and K. M. Snader, "Natural products as sources of new drugs over the period 1981–2002," *Journal of Natural Products*, vol. 66, no. 7, pp. 1022–1037, 2003.
- [105] D. Legros, G. Ollivier, M. Gastellu-Etchegorry et al., "Treatment of human African trypanosomiasis – present situation and needs for research and development," *The Lancet Infectious Diseases*, vol. 2, no. 7, pp. 437–440, 2002.
- [106] R. Brun, R. Schumacher, C. Schmid, C. Kunz, and C. Burri, "The phenomenon of treatment failures in human African trypanosomiasis," *Tropical Medicine & International Health*, vol. 6, no. 11, pp. 906–914, 2001.
- [107] L. Scotti, F. J. B. Mendonça, M. S. da Silva, and M. T. Scotti, "Enzymatic targets in *Trypanosoma brucei*," *Current Protein & Peptide Science*, vol. 17, no. 3, pp. 243–259, 2016.
- [108] A. Singh Grewal, D. Pandita, S. Bhardwaj, and V. Lather, "Recent updates on development of drug molecules for human African trypanosomiasis," *Current Topics in Medicinal Chemistry*, vol. 16, no. 20, pp. 2245–2265, 2016.
- [109] A. M. Clark, "Natural products as a resource for new drugs," *Pharmaceutical Research*, vol. 13, no. 8, pp. 1133–1141, 1996.
- [110] M. A. Ibrahim, A. Mohammed, M. B. Isah, and A. B. Aliyu, "Anti-trypanosomal activity of African medicinal plants: a review update," *Journal of Ethnopharmacology*, vol. 154, no. 1, pp. 26–54, 2014.
- [111] O. Oyeboode, N. B. Kandala, P. J. Chilton, and R. J. Lilford, "Use of traditional medicine in middle-income countries: a WHO-SAGE study," *Health Policy and Planning*, vol. 31, no. 8, pp. 984–991, 2016.
- [112] A. Nour, S. Khalid, M. Kaiser, R. Brun, W. Abdallah, and T. Schmidt, "The antiprotozoal activity of sixteen asteraceae species native to Sudan and bioactivity-guided isolation of xanthanolides from *Xanthium brasiliicum*," *Planta Medica*, vol. 75, no. 12, pp. 1363–1368, 2009.
- [113] M. R. Bockman, A. S. Kalinda, R. Petrelli et al., "Targeting *Mycobacterium tuberculosis* biotin protein ligase (MtBPL) with nucleoside-based bisubstrate adenylation inhibitors," *Journal of Medicinal Chemistry*, vol. 58, no. 18, pp. 7349–7369, 2015.
- [114] Y. Sun, J. No, G. Lee et al., "Phenolic constituents of medicinal plants with activity against *Trypanosoma brucei*," *Molecules*, vol. 21, no. 4, pp. 480–489, 2016.
- [115] N. Habila, A. S. Agbaji, Z. Ladan et al., "Evaluation of in vitro activity of essential oils against *Trypanosoma brucei brucei* and *Trypanosoma evansi*," *Journal of Parasitology Research*, vol. 2010, Article ID 534601, 5 pages, 2010.
- [116] G. Benelli, "Plant-borne ovicides in the fight against mosquito vectors of medical and veterinary importance: a systematic review," *Parasitology Research*, vol. 114, no. 9, pp. 3201–3212, 2015.
- [117] J. S. Raut and S. M. Karuppaiyl, "A status review on the medicinal properties of essential oils," *Industrial Crops and Products*, vol. 62, pp. 250–264, 2014.
- [118] R. Pavela and G. Benelli, "Essential oils as ecofriendly biopesticides? Challenges and constraints," *Trends in Plant Science*, vol. 21, no. 12, pp. 1000–1007, 2016.
- [119] G. V. B. Cruz, P. V. S. Pereira, F. J. Patrício et al., "Increase of cellular recruitment, phagocytosis ability and nitric oxide production induced by hydroalcoholic extract from *Chenopodium ambrosioides* leaves," *Journal of Ethnopharmacology*, vol. 111, no. 1, pp. 148–154, 2007.
- [120] L. Monzote, A. M. Montalvo, S. Almanonni, R. Scull, M. Miranda, and J. Abreu, "Activity of the essential oil from *Chenopodium ambrosioides* grown in Cuba against *Leishmania amazonensis*," *Chemotherapy*, vol. 52, no. 3, pp. 130–136, 2006.
- [121] J. Muhd Haffiz, I. Norhayati, K. Getha et al., "Chemical composition and *in vitro* antitrypanosomal activity of fractions of essential oil from *Cymbopogon nardus* L.," *Tropical Biomedicine*, vol. 30, no. 1, pp. 9–14, 2013.
- [122] S. Kpoviessi, J. Bero, P. Agbani et al., "Chemical composition, cytotoxicity and in vitro antitrypanosomal and antiplasmodial activity of the essential oils of four *Cymbopogon* species from Benin," *Journal of Ethnopharmacology*, vol. 151, no. 1, pp. 652–659, 2014.
- [123] B. G. H. Kpadonou Kpoviessi, S. D. S. Kpoviessi, E. Yayi Ladekan et al., "In vitro antitrypanosomal and antiplasmodial activities of crude extracts and essential oils of *Ocimum gratissimum* Linn from Benin and influence of vegetative stage," *Journal of Ethnopharmacology*, vol. 155, no. 3, pp. 1417–1423, 2014.
- [124] J. Bero, C. Beaufay, V. Hannaert, M.-F. Hérent, P. A. Michels, and J. Quetin-Leclercq, "Antitrypanosomal compounds from the essential oil and extracts of *Keetia leucantha* leaves with inhibitor activity on *Trypanosoma brucei* glyceraldehyde-3-phosphate dehydrogenase," *Phytomedicine*, vol. 20, no. 3–4, pp. 270–274, 2013.
- [125] D. P. de Sousa, T. Lima, and D. Steverding, "Evaluation of antiparasitic activity of *Mentha crispata* essential oil, its major constituent rotundifolone and analogues against *Trypanosoma brucei*," *Planta Medica*, vol. 82, no. 15, pp. 1346–1350, 2016.
- [126] Y. Gutiérrez, R. Montes, R. Scull et al., "Chemodiversity associated with cytotoxicity and antimicrobial activity of *Piper aduncum* var. *ossanum*," *Chemistry & Biodiversity*, vol. 13, no. 12, pp. 1715–1719, 2016.
- [127] V. S. Parmar, S. C. Jain, K. S. Bisht et al., "Phytochemistry of the genus *Piper*," *Phytochemistry*, vol. 46, no. 4, pp. 597–673, 1997.
- [128] H. D. Neuwinger, *African Traditional Medicine: a Dictionary of Plant Use and Applications*, Medpharm, Stuttgart, 2000.
- [129] S. Hoet, C. Stévigny, M.-F. Hérent, and J. Quetin-Leclercq, "Antitrypanosomal compounds from the leaf essential oil of *Strychnos spinosa*," *Planta Medica*, vol. 72, no. 5, pp. 480–482, 2006.
- [130] S. Mulyaningsih, M. Youns, M. Z. El-Readi et al., "Biological activity of the essential oil of *Kadsura longipedunculata* (Schisandraceae) and its major components," *Journal of Pharmacy and Pharmacology*, vol. 62, no. 8, pp. 1037–1044, 2010.
- [131] D. Hamdan, M. Z. El-Readi, E. Nibret et al., "Chemical composition of the essential oils of two Citrus species and their biological activities," *Pharmazie*, vol. 65, no. 2, pp. 141–147, 2010.

- [132] R. Petrelli, G. Orsomando, L. Sorci et al., "Biological activities of the essential oil from *Erigeron floribundus*," *Molecules*, vol. 21, no. 8, pp. 1065–1078, 2016.
- [133] Z. Cheikh-Ali, M. Adiko, S. Bouttier et al., "Composition, and antimicrobial and remarkable antiprotozoal activities of the essential oil of rhizomes of *Aframomum sceptrum* K. Schum (Zingiberaceae)," *Chemistry & Biodiversity*, vol. 8, no. 4, pp. 658–667, 2011.
- [134] F. Herrmann, R. Hamoud, F. Sporer, A. Tahrani, and M. Wink, "Carlina oxide – a natural polyacetylene from *Carlina acaulis* (Asteraceae) with potent antitrypanosomal and antimicrobial properties," *Planta Medica*, vol. 77, no. 17, pp. 1905–1911, 2011.
- [135] S. L. Nghanh Kamte, F. Ranjbarian, K. Cianfaglione et al., "Identification of highly effective antitrypanosomal compounds in essential oils from the Apiaceae family," *Ecotoxicology and Environmental Safety*, vol. 156, pp. 154–165, 2018.
- [136] F. Maggi, L. Barboni, F. Papa et al., "A forgotten vegetable (*Smyrniium olusatrum* L., Apiaceae) as a rich source of isofuranodiene," *Food Chemistry*, vol. 135, no. 4, pp. 2852–2862, 2012.
- [137] F. Maggi, F. Papa, C. Giuliani et al., "Essential oil chemotypification and secretory structures of the neglected vegetable *Smyrniium olusatrum* L. (Apiaceae) growing in central Italy," *Flavour and Fragrance Journal*, vol. 30, no. 2, pp. 139–159, 2015.
- [138] F. Maggi, F. Papa, S. Pucciarelli et al., "Stabilization of the cyclodecadiene derivative isofuranodiene by silver (I) coordination. Mechanistic and biological aspects," *Fitoterapia*, vol. 117, pp. 52–60, 2017.
- [139] K. A. d. F. Rodrigues, C. N. d. S. Dias, P. L. d. N. Nêris et al., "2-Amino-thiophene derivatives present antileishmanial activity mediated by apoptosis and immunomodulation in vitro," *European Journal of Medicinal Chemistry*, vol. 106, pp. 1–14, 2015.
- [140] M. B. Félix, E. R. de Souza, M. D. C. A. de Lima et al., "Antileishmanial activity of new thiophene-indole hybrids: design, synthesis biological and cytotoxic evaluation, and chemometric studies," *Bioorganic & Medicinal Chemistry*, vol. 24, no. 18, pp. 3972–3977, 2016.
- [141] D. J. Brondani and L. S. da Silva Junior, "A química medicinal das Leishmanioses," in *Doenças Negligenciadas sob a ótica da Química Medicinal*, pp. 203–260, CRV, Curitiba/Parana-Brazil, 1st edition edition, 2015.
- [142] K. Katsuno, J. N. Burrows, K. Duncan et al., "Hit and lead criteria in drug discovery for infectious diseases of the developing world," *Nature Reviews Drug Discovery*, vol. 14, no. 11, pp. 751–758, 2015.
- [143] S. B. H. Ahmed, R. M. Sghaier, F. Guesmi et al., "Evaluation of antileishmanial, cytotoxic and antioxidant activities of essential oils extracted from plants issued from the leishmaniasis-endemic region of Sned (Tunisia)," *Natural Product Research*, vol. 25, no. 12, pp. 1195–1201, 2011.
- [144] M. A. Andrade, C. S. Azevedo, F. N. Motta et al., "Essential oils: in vitro activity against *Leishmania amazonensis*, cytotoxicity and chemical composition," *BMC Complementary and Alternative Medicine*, vol. 16, no. 1, pp. 444–448, 2016.
- [145] R. R. P. Machado, W. Valente Júnior, B. Lesche et al., "Essential oil from leaves of *Lantana camara*: a potential source of medicine against leishmaniasis," *Revista Brasileira de Farmacognosia*, vol. 22, no. 5, pp. 1011–1017, 2012.
- [146] A. Gawde, C. L. Cantrell, V. D. Zheljzkov, T. Astatkie, and V. Schlegel, "Steam distillation extraction kinetics regression models to predict essential oil yield, composition, and bioactivity of chamomile oil," *Industrial Crops and Products*, vol. 58, pp. 61–67, 2014.
- [147] J. M. Rodilla, L. A. Silva, N. Martinez et al., "Advances in the identification and agrochemical importance of sesquiterpenoids from *Bulnesia sarmientoi* essential oil," *Industrial Crops and Products*, vol. 33, no. 2, pp. 497–503, 2011.
- [148] L. Kuźma, D. Kalembe, M. Różalski et al., "Chemical composition and biological activities of essential oil from *Salvia sclarea* plants regenerated in vitro," *Molecules*, vol. 14, no. 4, pp. 1438–1447, 2009.
- [149] L. P. Kvist, S. B. Christensen, H. B. Rasmussen, K. Mejia, and A. Gonzalez, "Identification and evaluation of Peruvian plants used to treat malaria and leishmaniasis," *Journal of Ethnopharmacology*, vol. 106, no. 3, pp. 390–402, 2006.
- [150] R. d. C. R. Moreira, J. M. M. Rebêlo, M. E. A. Gama, and J. M. L. Costa, "Awareness of American tegumentary leishmaniasis (ATL) and use of alternative therapies in an endemic area in the Amazon Region in the State of Maranhão, Brazil," *Cadernos de Saúde Pública*, vol. 18, no. 1, pp. 187–195, 2002.
- [151] M. Fleury, "À propos de l'intérêt médicinal du baume de Copahu," *Acta Botanica Gallica*, vol. 144, no. 4, pp. 473–479, 1997.
- [152] P. Grenand, C. Moretti, and H. Jacquemin, *Pharmacopées Traditionnelles en Guyane*, Éditions de IORSTOM, 2014.
- [153] A. O. Santos, T. Ueda-Nakamura, B. P. Dias Filho, V. F. Veiga Junior, A. C. Pinto, and C. V. Nakamura, "Effect of Brazilian copaiba oils on *Leishmania amazonensis*," *Journal of Ethnopharmacology*, vol. 120, no. 2, pp. 204–208, 2008.
- [154] N. M. Gomes, C. M. Rezende, S. P. Fontes, M. E. Matheus, and P. D. Fernandes, "Antinociceptive activity of Amazonian copaiba oils," *Journal of Ethnopharmacology*, vol. 109, no. 3, pp. 486–492, 2007.
- [155] V. F. Veiga Junior, E. C. Rosas, M. V. Carvalho, M. G. M. O. Henriques, and A. C. Pinto, "Chemical composition and anti-inflammatory activity of copaiba oils from *Copaifera cearensis* Huber ex Ducke, *Copaifera reticulata* Ducke and *Copaifera multijuga* Hayne—a comparative study," *Journal of Ethnopharmacology*, vol. 112, no. 2, pp. 248–254, 2007.
- [156] A. O. dos Santos, M. A. Costa, T. Ueda-Nakamura et al., "*Leishmania amazonensis*: effects of oral treatment with copaiba oil in mice," *Experimental Parasitology*, vol. 129, no. 2, pp. 145–151, 2011.
- [157] D. C. Soares, N. A. Portella, M. F. S. Ramos, A. C. Siani, and E. M. Saraiva, "Trans- β -caryophyllene: an effective antileishmanial compound found in commercial copaiba oil (*Copaifera* spp.)," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 761323, 13 pages, 2013.
- [158] Y. Tariku, A. Hymete, A. Hailu, and J. Rohloff, "In vitro evaluation of antileishmanial activity and toxicity of essential oils of *Artemisia absinthium* and *Echinops kebericho*," *Chemistry & Biodiversity*, vol. 8, no. 4, pp. 614–623, 2011.
- [159] Y. Tariku, A. Hymete, A. Hailu, and J. Rohloff, "Essential-oil composition, antileishmanial, and toxicity study of *Artemisia abyssinica* and *Satureja punctata* ssp. *punctata* from Ethiopia," *Chemistry & Biodiversity*, vol. 7, no. 4, pp. 1009–1018, 2010.
- [160] V. D. da Silva, F. Almeida-Souza, A. M. Teles et al., "Chemical composition of *Ocimum canum* Sims. essential oil and the

- antimicrobial, antiprotozoal and ultrastructural alterations it induces in *Leishmania amazonensis* promastigotes,” *Industrial Crops and Products*, vol. 119, pp. 201–208, 2018.
- [161] A. O. Santos, A. C. Santin, M. U. Yamaguchi et al., “Antileishmanial activity of an essential oil from the leaves and flowers of *Achillea millefolium*,” *Annals of Tropical Medicine & Parasitology*, vol. 104, no. 6, pp. 475–483, 2010.
- [162] M. D. S. S. Rosa, R. R. Mendonca-Filho, H. R. Bizzo et al., “Antileishmanial activity of a linalool-rich essential oil from *Croton cajucara*,” *Antimicrobial Agents and Chemotherapy*, vol. 47, no. 6, pp. 1895–1901, 2003.
- [163] M. Islamuddin, G. Chouhan, M. Tyagi, M. Z. Abdin, D. Sahal, and F. Afrin, “Leishmanicidal activities of *Artemisia annua* leaf essential oil against Visceral Leishmaniasis,” *Frontiers in Microbiology*, vol. 5, p. 626, 2014.
- [164] I. A. Rodrigues, M. M. B. Azevedo, F. C. M. Chaves et al., “*In vitro* cytotoxic effects of the essential oil from *Croton cajucara* (red sacaca) and its major constituent 7-hydroxycalamenene against *Leishmania chagasi*,” *BMC Complementary and Alternative Medicine*, vol. 13, no. 1, p. 249, 2013.
- [165] T. Ueda-Nakamura, R. R. Mendonça-Filho, J. A. Morgado-Díaz et al., “Antileishmanial activity of eugenol-rich essential oil from *Ocimum gratissimum*,” *Parasitology International*, vol. 55, no. 2, pp. 99–105, 2006.
- [166] F. L. Dutra, M. M. Oliveira, R. S. Santos et al., “Effects of linalool and eugenol on the survival of *Leishmania (L.) infantum chagasi* within macrophages,” *Acta Tropica*, vol. 164, pp. 69–76, 2016.
- [167] M. R. Santin, A. O. dos Santos, C. V. Nakamura, B. P. Dias Filho, I. C. P. Ferreira, and T. Ueda-Nakamura, “*In vitro* activity of the essential oil of *Cymbopogon citratus* and its major component (citral) on *Leishmania amazonensis*,” *Parasitology Research*, vol. 105, no. 6, pp. 1489–1496, 2009.
- [168] K. A. d. F. Rodrigues, L. V. Amorim, J. M. G. d. Oliveira et al., “*Eugenia uniflora* L. essential oil as a potential anti-*Leishmania* agent: effects on *Leishmania amazonensis* and possible mechanisms of action,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 279726, 10 pages, 2013.
- [169] K. A. d. F. Rodrigues, L. V. Amorim, C. N. Dias, D. F. C. Moraes, S. M. P. Carneiro, and F. A. d. A. Carvalho, “*Syzygium cumini* (L.) Skeels essential oil and its major constituent α -pinene exhibit anti-*Leishmania* activity through immunomodulation *in vitro*,” *Journal of Ethnopharmacology*, vol. 160, pp. 32–40, 2015.
- [170] L. S. S. Bosquiroli, D. P. Demarque, Y. S. Rizk et al., “*In vitro* anti-*Leishmania infantum* activity of essential oil from *Piper angustifolium*,” *Revista Brasileira de Farmacognosia*, vol. 25, no. 2, pp. 124–128, 2015.
- [171] A. Bouyahya, A. Et-Touys, J. Abrini et al., “*Lavandula stoechas* essential oil from Morocco as novel source of antileishmanial, antibacterial and antioxidant activities,” *Biocatalysis and Agricultural Biotechnology*, vol. 12, pp. 179–184, 2017.
- [172] A. Bouyahya, A. Et-Touys, Y. Bakri et al., “Chemical composition of *Mentha pulegium* and *Rosmarinus officinalis* essential oils and their antileishmanial, antibacterial and antioxidant activities,” *Microbial Pathogenesis*, vol. 111, pp. 41–49, 2017.
- [173] A. Bouyahya, N. Dakka, A. Talbaoui et al., “Correlation between phenological changes, chemical composition and biological activities of the essential oil from Moroccan endemic Oregano (*Origanum compactum* Benth),” *Industrial Crops and Products*, vol. 108, pp. 729–737, 2017.
- [174] R. Essid, F. Z. Rahali, K. Msaada et al., “Antileishmanial and cytotoxic potential of essential oils from medicinal plants in Northern Tunisia,” *Industrial Crops and Products*, vol. 77, pp. 795–802, 2015.
- [175] I. G. Demarchi, M. S. Terron, M. V. Thomazella et al., “Antileishmanial and immunomodulatory effects of the essential oil from *Tetradenia riparia* (Hochstetter) Codd,” *Parasite Immunology*, vol. 38, no. 1, pp. 64–77, 2016.
- [176] L. Monzote, A. M. Montalvo, R. Scull, M. Miranda, and J. Abreu, “Combined effect of the essential oil from *Chenopodium ambrosioides* and antileishmanial drugs on promastigotes of *Leishmania amazonensis*,” *Revista do Instituto de Medicina Tropical de São Paulo*, vol. 49, no. 4, pp. 257–260, 2007.
- [177] L. Monzote, M. García, A. M. Montalvo, R. Scull, M. Miranda, and J. Abreu, “*In vitro* activity of an essential oil against *Leishmania donovani*,” *Phytotherapy Research*, vol. 21, no. 11, pp. 1055–1058, 2007.
- [178] L. Monzote, A. M. Montalvo, R. Scull, M. Miranda, and J. Abreu, “Activity, toxicity and analysis of resistance of essential oil from *Chenopodium ambrosioides* after intraperitoneal, oral and intralesional administration in BALB/c mice infected with *Leishmania amazonensis*: a preliminary study,” *Biomedicine & Pharmacotherapy*, vol. 61, no. 2–3, pp. 148–153, 2007.
- [179] L. Monzote, M. García, A. M. Montalvo, R. Linares, and R. Scull, “Effect of oral treatment with the essential oil from *Chenopodium ambrosioides* against cutaneous Leishmaniasis in BALB/c mice, caused by *Leishmania amazonensis*,” *Forschende Komplementärmedizin/Research in Complementary Medicine*, vol. 16, no. 5, pp. 334–338, 2009.
- [180] L. Monzote, J. Pastor, R. Scull, and L. Gille, “Antileishmanial activity of essential oil from *Chenopodium ambrosioides* and its main components against experimental cutaneous leishmaniasis in BALB/c mice,” *Phytomedicine*, vol. 21, no. 8–9, pp. 1048–1052, 2014.
- [181] L. Monzote, M. García, R. Scull, A. Cuellar, and W. N. Setzer, “Antileishmanial activity of the essential oil from *Bixa orellana*,” *Phytotherapy Research*, vol. 28, no. 5, pp. 753–758, 2014.
- [182] L. Monzote, G. Geroldinger, M. Tonner et al., “Interaction of ascaridole, carvacrol, and caryophyllene oxide from essential oil of *Chenopodium ambrosioides* L. with mitochondria in *Leishmania* and other eukaryotes,” *Phytotherapy Research*, vol. 32, no. 9, pp. 1729–1740, 2018.
- [183] A. V. Colares, F. Almeida-Souza, N. N. Taniwaki et al., “*In vitro* antileishmanial activity of essential oil of *Vanillosmopsis arborea* (Asteraceae) Baker,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 727042, 7 pages, 2013.
- [184] R. Tisserand and T. Balacs, *Essential Oil Safety: A Guide for Health Care Professionals*, Churchill Livingstone, 1st edition, 1995.
- [185] M. Morales-Yuste, F. Morillas-Márquez, J. Martín-Sánchez, A. Valero-López, and M. C. Navarro-Moll, “Activity of (α)-bisabolol against *Leishmania infantum* promastigotes,” *Phytomedicine*, vol. 17, no. 3–4, pp. 279–281, 2010.
- [186] F. Xavier, K. Rodrigues, R. de Oliveira et al., “Synthesis and *in vitro* anti *Leishmania amazonensis* biological screening of Morita-Baylis-Hillman adducts prepared from eugenol, thymol and carvacrol,” *Molecules*, vol. 21, no. 11, article 1483, 2016.

- [187] A. Silva, R. Scher, F. Santos et al., "Leishmanicidal activity and structure-activity relationships of essential oil constituents," *Molecules*, vol. 22, no. 5, p. 815, 2017.
- [188] S. M. de Moraes, N. S. Vila-Nova, C. M. L. Bevilacqua et al., "Thymol and eugenol derivatives as potential antileishmanial agents," *Bioorganic & Medicinal Chemistry*, vol. 22, no. 21, pp. 6250–6255, 2014.
- [189] P. A. Farias-Junior, M. C. Rios, T. A. Moura et al., "Leishmanicidal activity of carvacrol-rich essential oil from *Lippia sidoides* cham," *Biological Research*, vol. 45, no. 4, pp. 399–402, 2012.
- [190] E. Houël, G. Gonzalez, J. M. Bessière et al., "Therapeutic switching: from antidermatophytic essential oils to new leishmanicidal products," *Memórias do Instituto Oswaldo Cruz*, vol. 110, no. 1, pp. 106–113, 2015.
- [191] B. M. Cardoso, T. F. P. Mello, S. N. Lopes et al., "Antileishmanial activity of the essential oil from *Tetradenia riparia* obtained in different seasons," *Memórias do Instituto Oswaldo Cruz*, vol. 110, no. 8, pp. 1024–1034, 2015.
- [192] I. G. Demarchi, M. V. Thomazella, M. de Souza Terron et al., "Antileishmanial activity of essential oil and 6,7-dehydroroyleanone isolated from *Tetradenia riparia*," *Experimental Parasitology*, vol. 157, pp. 128–137, 2015.
- [193] R. Yesmit Karina Ríos, J. Astrid Carolina Otero, H. Diana Lorena Muñoz, R. Mónica Echeverry, R. Sara María Robledo, and C. Maira Alejandra Yepes, "Actividad citotóxica y leishmanicida *in vitro* del aceite esencial de manzanilla (*Matricaria chamomilla*)," *Revista Colombiana de Ciencias Químico-Farmacéuticas*, vol. 37, no. 2, pp. 200–211, 2008.
- [194] N. Q. M. Al-Hajj, H. Wang, M. A. A. Gasmalla et al., "Chemical composition and antioxidant activity of the essential oil of *Pulicaria inuloides*," *Journal of Food and Nutrition Research*, vol. 2, no. 5, pp. 221–227, 2014.
- [195] H. Mahmoudvand, F. Ezzatkah, F. Shariffar, I. Sharifi, and E. S. Dezaki, "Antileishmanial and cytotoxic effects of essential oil and methanolic extract of *Myrtus communis* L.," *The Korean Journal of Parasitology*, vol. 53, no. 1, pp. 21–27, 2015.
- [196] L. F. Neira, E. Stashenko, and P. Escobar, "Actividad antiparasitaria de extractos de plantas colombianas de la familia Euphorbiaceae," *Revista de la Universidad Industrial de Santander. Salud*, vol. 46, no. 1, pp. 15–22, 2014.
- [197] E. V. Costa, M. L. B. Pinheiro, J. R. d. A. Silva et al., "Antimicrobial and antileishmanial activity of essential oil from the leaves of *Annona foetida* (Annonaceae)," *Química Nova*, vol. 32, no. 1, pp. 78–81, 2009.
- [198] R. López, L. E. Cuca, and G. Delgado, "Antileishmanial and immunomodulatory activity of *Xylopiya discreta*," *Parasite Immunology*, vol. 31, no. 10, pp. 623–630, 2009.
- [199] E. B. B. Estevam, I. P. B. D. Deus, V. P. D. Silva et al., "In vitro antiparasitic activity and chemical composition of the essential oil from *Protium ovatum* leaves (Burceraceae)," *Anais da Academia Brasileira de Ciências*, vol. 89, no. 4, pp. 3005–3013, 2017.
- [200] J. O. de Melo, T. A. Bitencourt, A. L. Fachin et al., "Antidermatophytic and antileishmanial activities of essential oils from *Lippia gracilis* Schauer genotypes," *Acta Tropica*, vol. 128, no. 1, pp. 110–115, 2013.
- [201] A. Uniyal, S. N. Tikar, R. Singh et al., "Synergic effect of effective oils against *Aedes aegypti* female mosquito, vector of dengue and chikungunya," *International Journal of Mosquito Research*, vol. 2, no. 4, pp. 29–35, 2015.
- [202] M. Soonwera, "Efficacy of essential oils from Citrus plants against mosquito vector *Aedes aegypti* (Linn) and *Culex quinquefasciatus* (Say)," *Journal of Agricultural Technology*, vol. 11, no. 3, pp. 669–681, 2015.
- [203] F. Manzoor, K. B. Samreen, and Z. Parveen, "Larvicidal activity of essential oils against *Aedes aegypti* and *Culex quinquefasciatus* larvae (Diptera Culicidae)," *The Journal of Animal & Plant Sciences*, vol. 23, no. 2, pp. 420–424, 2013.
- [204] C. N. Dias and D. F. C. Moraes, "Essential oils and their compounds as *Aedes aegypti* L. (Diptera Culicidae) larvicides: review," *Parasitology Research*, vol. 113, no. 2, pp. 565–592, 2014.
- [205] H. S. Santos, P. N. Bandeira, T. L. G. Lemos, and G. M. P. Santiago, "Chemical composition and larvicidal activity against *Aedes aegypti* L. (Diptera: Culicidae) of essential oils from leaves, stalks and roots of the *Croton nepetaefolius* Baill (Euphorbiaceae)," *International Journal of Mosquito Research*, vol. 4, no. 5, pp. 19–22, 2017.
- [206] D. Navarro, P. Silva, M. Silva, T. Napoleao, and P. Paiva, "Larvicidal activity of plant and algae extracts, essential oils and isolated chemical constituents against *Aedes aegypti*," *The Natural Products Journal*, vol. 3, no. 4, pp. 268–291, 2014.
- [207] G. L. Oliveira, S. K. Cardoso, C. R. Lara Junior et al., "Chemical study and larvicidal activity against *Aedes Aegypti* of essential oil of *Piper aduncum* L. (Piperaceae)," *Anais da Academia Brasileira de Ciências*, vol. 85, no. 4, pp. 1227–1234, 2013.
- [208] F. Manzoor, K. B. Samreen, and Z. Parveen, "Larvicidal activity of essential oils against *Aedes aegypti* and *Culex quinquefasciatus* larvae (Diptera: Culicidae)," *The Journal of Animal & Plant Sciences*, vol. 23, no. 2, pp. 420–424, 2013.
- [209] M. Soonwera, "Efficacy of essential oils from Citrus plants against mosquito vectors *Aedes aegypti* (Linn.) and *Culex quinquefasciatus* (Say)," *International Journal of Agricultural Technology*, vol. 11, no. 3, pp. 669–681, 2015.
- [210] A. F. d. O. Araujo, J. T. Ribeiro-Paes, J. T. d. Deus et al., "Larvicidal activity of *Syzygium aromaticum* (L.) Merr and *Citrus sinensis* (L.) Osbeck essential oils and their antagonistic effects with temephos in resistant populations of *Aedes aegypti*," *Memórias do Instituto Oswaldo Cruz*, vol. 111, no. 7, pp. 443–449, 2016.
- [211] D. Sritabutra, M. Soonwera, S. Waltanachanobon, and S. Pongjai, "Evaluation of herbal essential oil as repellents against *Aedes aegypti* (L.) and *Anopheles dirus* Peyton & Harrison," *Asian Pacific Journal of Tropical Biomedicine*, vol. 1, no. 1, pp. S124–S128, 2011.
- [212] S. Zhu, X. C. Liu, Z. L. Liu, and X. Xu, "Chemical composition of *Salvia plebeian* R. Br. essential oil and its larvicidal activity against *Aedes aegypti* L.," *Tropical Journal of Pharmaceutical Research*, vol. 14, no. 5, pp. 831–836, 2015.
- [213] S.-S. Cheng, M.-T. Chua, K.-H. Tsai, W.-J. Chen, and S.-T. Chang, "Chemical composition and mosquito larvicidal activity of essential oils from leaf of *Cryptomeria japonica*," 2013, http://gra103.aca.ntu.edu.tw/gdoc/94/d89625006a.pdf?origin=publication_detail.
- [214] S. R. L. Santos, M. A. Melo, A. V. Cardoso, R. L. C. Santos, D. P. de Sousa, and S. C. H. Cavalcanti, "Structure-activity relationships of larvicidal monoterpenes and derivatives against *Aedes aegypti* Linn," *Chemosphere*, vol. 84, no. 1, pp. 150–153, 2011.
- [215] S. S. Cheng, M. T. Chua, E. H. Chang, C. G. Huang, W. J. Chen, and S. T. Chang, "Variations in insecticidal activity

- and chemical compositions of leaf essential oils from *Cryptomeria japonica* at different ages,” *Bioresource Technology*, vol. 100, no. 1, pp. 465–470, 2009.
- [216] S. S. Cheng, C. G. Huang, Y. J. Chen, J. J. Yu, W. J. Chen, and S. T. Chang, “Chemical compositions and larvicidal activities of leaf essential oils from two eucalyptus species,” *Bioresource Technology*, vol. 100, no. 1, pp. 452–456, 2009.
- [217] S. R. L. Santos, V. B. Silva, M. A. Melo et al., “Toxic effects on and structure-toxicity relationships of phenylpropanoids, terpenes, and related compounds in *Aedes aegypti* larvae,” *Vector-Borne and Zoonotic Diseases*, vol. 10, no. 10, pp. 1049–1054, 2010.
- [218] N. Tabanca, C. Avonto, M. Wang et al., “Comparative investigation of *Umbellularia californica* and *Laurus nobilis* leaf essential oils and identification of constituents active against *Aedes aegypti*,” *Journal of Agricultural and Food Chemistry*, vol. 61, no. 50, pp. 12283–12291, 2013.
- [219] D. K. Rocha, O. Matosc, M. T. Novoa, A. C. Figueiredo, M. Delgado, and C. Moiteiro, “Larvicidal activity against *Aedes aegypti* of *Foeniculum vulgare* essential oils from Portugal and Cape Verde,” *Natural Product Communications*, vol. 10, no. 4, pp. 677–682, 2015.
- [220] T. C. Lima, T. K. M. da Silva, F. L. Silva et al., “Larvicidal activity of *Mentha x villosa* Hudson essential oil, rotundifolone and derivatives,” *Chemosphere*, vol. 104, pp. 37–43, 2014.
- [221] N. Tabanca, Z. Gao, B. Demirci et al., “Molecular and phytochemical investigation of *Angelica dahurica* and *Angelica pubescentis* essential oils and their biological activity against *Aedes aegypti*, *stephanitis pyrioides*, and *colletotrichum* species,” *Journal of Agricultural and Food Chemistry*, vol. 62, no. 35, pp. 8848–8857, 2014.
- [222] G. Santos, K. Dutra, C. Lira et al., “Effects of *Croton rhamnifolioides* essential oil on *Aedes aegypti* oviposition, larval toxicity and trypsin activity,” *Molecules*, vol. 19, no. 10, pp. 16573–16587, 2014.
- [223] N. Tabanca, U. R. Bernier, A. Ali et al., “Bioassay-guided investigation of two *Monarda* essential oils as repellents of yellow fever mosquito *Aedes aegypti*,” *Journal of Agricultural and Food Chemistry*, vol. 61, no. 36, pp. 8573–8580, 2013.
- [224] J. D. Barbosa, V. B. Silva, P. B. Alves et al., “Structure-activity relationships of eugenol derivatives against *Aedes aegypti* (Diptera: Culicidae) larvae,” *Pest Management Science*, vol. 68, no. 11, pp. 1478–1483, 2012.
- [225] I. M. Chung, H. K. Song, M. A. Yeo, and H. I. Moon, “Composition and immunotoxicity activity of major essential oils from stems of *Allium victorialis* L. var. *Platyphyllum* makino against *Aedes aegypti* L,” *Immunopharmacology and Immunotoxicology*, vol. 33, no. 3, pp. 480–483, 2010.
- [226] H. I. Moon, “Larvicidal activity of major essential oils from stems of *Allium monanthum* Maxim. against *Aedes aegypti* L,” *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 26, no. 6, pp. 827–830, 2011.
- [227] V. B. Silva, D. L. Travassos, A. Nepel et al., “Synthesis and chemometrics of thymol and carvacrol derivatives as larvicides against *Aedes aegypti*,” *Journal of Arthropod-Borne Diseases*, vol. 11, no. 2, pp. 305–320, 2017.
- [228] L. Scotti, M. Scotti, V. Silva, S. Santos, S. Cavalcanti, and F. Junior, “Chemometric studies on potential larvicidal compounds against *Aedes aegypti*,” *Medicinal Chemistry*, vol. 10, no. 2, pp. 201–210, 2014.



Hindawi

Submit your manuscripts at
www.hindawi.com

