Chapter 13
Antileishmanial Activity of Essential Oils

José Weverton Almeida-Bezerra, Victor Juno Alencar Fonseca, Johnatan Wellisson da Silva Mendes, Roberta Dávila Pereira de Lima, Antonia Thassya Lucas dos Santos, Saulo Almeida de Menezes, Benedito Yago Machado Portela, Lilian Cortez Sombra Vandesmet, Felicidade Caroline Rodrigues, José Jailson Lima Bezerra, Viviane Bezerra da Silva, Rafael Pereira da Cruz, Allyson Francisco dos Santos, Cícero Jorge Verçosa, Jamile Maria Pereira Bastos Lira de Vasconcelos, Maria Eliana Vieira Figueroa, Clêidio da Paz Cabral, Gabriel Messias da Silva Nascimento, Maria Ivaneide Rocha, Marcio Pereira do Nascimento, Priscilla Augusta de Sousa Fernandes, Francisco Sydney Henrique da Silva, and Maria Flaviana Bezerra Morais-Braga

13.1 Introduction

Besides being an important component of the plant defense system against pathogenic attacks and environmental stress, the secondary metabolism of plants provides a useful range of natural products (Piasecka et al. 2015). Due to their biological

J. W. Almeida-Bezerra (✉) · V. J. A. Fonseca · J. W. da Silva Mendes · A. T. L. dos Santos · R. P. da Cruz · G. M. da Silva Nascimento · M. I. Rocha · M. P. do Nascimento · P. A. de Sousa Fernandes · M. F. B. Morais-Braga
Regional University of Cariri – URCA, Crato, CE, Brazil
e-mail: weverton.almeida@urca.br

R. D. P. de Lima
Federal University of Cariri – UFCA, Crato, CE, Brazil

S. A. de Menezes
Federal University of Rio Grande do Sul – UFRGS, Porto Alegre, RS, Brazil

B. Y. M. Portela
Federal University of Ceara – UFC, Fortaleza, CE, Brazil

L. C. S. Vandesmet
Catholic University Center of Quixadá, Quixadá, CE, Brazil

F. C. Rodrigues · J. J. L. Bezerra · V. B. da Silva
Federal University of Pernambuco – UFPE, Recife, PE, Brazil

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activities, the secondary metabolites of plants have been increasingly used as medicinal substances and food additives for therapeutic, aromatic and culinary purposes. The characteristics and concentration of secondary molecules and the biosynthesis by a plant are defined by the identity of the species and genetic, ontogenic, morphogenetic, physiological, developmental, and environmental factors. This suggests that various taxonomic groups of plants have adaptive physiological responses to deal with stress and defensive stimuli (Yang et al. 2018; Isah 2019).

Terpenes and terpenoids (the oxygenated derivatives of terpenes) are chemical compounds that represent the majority of molecules in the composition of essential oils (EOs) (Matos et al. 2019). This class of molecules is characterized by a different number of isoprene (C_5H_8) units (Blowman et al. 2018). Depending on the number of these units, terpenes can be categorized into hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, triterpenes, among others (Rubulotta and Quadrelli 2019; Sharma et al. 2021). They can also be divided into groups such as acyclic, monocyclic, and bicyclic (Blowman et al. 2018). The terpenoid is a type of terpene that has oxygen attached to its structure (Sharma et al. 2021).

Essential oils, which are one of the substance types formed by terpenes, are widely used and studied for their pharmacological, biological, and permeation enhancing properties. However, several terpenes and EOs are sensitive to environmental conditions and may undergo volatilization and chemical degradation (Matos et al. 2019). Essential oils are natural products with a complex composition and are used in different ways, namely, through inhalation, topical application onto the skin, and oral consumption. There are, therefore, three main routes of ingestion or application: the skin system, the olfactory system, and the gastrointestinal system. Understanding these routes is important to clarify the mechanisms of action of EOs (Koyama and Heinbockel 2020).

The biological and pharmacological activities of EOs investigated so far include antibacterial (Ács et al. 2018), antifungal (Mutlu-Ingok et al. 2020), antiviral (Brochot et al. 2017), antileishmanial (Oliveira et al. 2020), antioxidant (Menezes Filho et al. 2020), cytotoxic (Contini et al. 2020), and anti-inflammatory (Saldanha et al. 2019) activities.

Leishmaniasis is a collection of diseases caused by parasitic protozoa of more than 20 species of *Leishmania*. The disease has three main forms: the tegumentary (most common form), the visceral (most severe form), and the mucocutaneous (most disabling form). Humans are contaminated by these parasites by the bite of infected female phlebotomine sandflies (WHO 2021). The clinical manifestations of leishmaniasis are quite mutable and can range from localized skin lesions to dissipation of life-threatening visceral disease (Meira and Gedamu 2019). Currently,

A. F. dos Santos · C. J. Verçosa · J. M. P. B. L. de Vasconcelos · M. E. V. Figueroa · C. da Paz Cabral
Pernambuco Department of Education and Sports, Recife, PE, Brazil

F. S. H. da Silva
State University of Ceará – UECE, Fortaleza, CE, Brazil

more than 1 billion people worldwide are in endemic areas of leishmaniasis and are at risk of infection (WHO 2021).

The first-line drugs for the treatment of leishmaniasis are antimonials. In resistant cases, pentavalents, amphotericin B deoxycholate, liposomal amphotericin B, and paromomycin are used as secondary options. However, these drugs have their use limited because of side effects, high costs, induction of resistance in parasites, and administration in hospitalized patients (Albuquerque et al. 2020). Therefore, research for new compounds is needed. In this sense, EOs have been increasingly investigated for their effectiveness against species of the genus *Leishmania*, to serve as an alternative for the treatment of leishmaniasis (Mahmoudvand et al. 2016; Sharifi-Rad et al. 2018; Rottini et al. 2019; Macêdo et al. 2020; Ferreira et al. 2020; Vandesmet et al. 2020; Gomez et al. 2021).

Therefore, this review seeks to understand the action of EOs against *Leishmania* species, parasites that cause vector-borne diseases known as leishmaniasis and which represent a serious public health problem.

13.2 Methodology

13.2.1 Database Search

Articles were searched through consultations in the Scopus© database (https://www.scopus.com/). As keywords, the descriptors "Essential oil AND *Leishmania*" were used, only in the English language.

13.2.2 Inclusion and Exclusion Criteria

Only scientific articles that addressed specific information about the potential of EOs extracted from different plant species against *Leishmania* spp. and published in the last 10 years (2011–2021) were selected. Regarding the exclusion criteria, review articles, e-books, book chapters, editorials, course completion works, dissertations, theses, abstracts published in congress proceedings, and articles on the potential of extracts, isolated chemical compounds, EOs commercialized without identification of the species, non-active EOs, and fixed oils against *Leishmania* spp. were discarded.

13.2.3 Data Screening and Information Categorization

Initially, 186 scientific articles were identified and selected in the Scopus© database. After applying the exclusion criteria, 72 documents that did not fit the theme of this review were discarded (Fig. 13.1). Finally, 114 articles containing data on the

potential of EOs against *Leishmania* spp. were included (Fig. 13.1). The information collected in the articles was categorized into: (1) "Essential oils against *Leishmania* spp."; (2) "Terpenes"; (3) "Mechanisms of action"; (4) "Other compounds present in essential oils"; and (5) "Other applications". Further details about the species, active concentration of essential oils, evolutionary form of *Leishmania* spp., major constituents, and mechanism of action were also organized and presented in a table.

13.3 Results

Of 186 articles, 114 met the inclusion criteria and were selected for data extraction (Table 13.1). Of the 114 studies, 111 are *in vitro* (97.4%), 2 *in vivo/in vitro* (1.7%), and 1 *in vivo* (0.9%) assays of EOs with leishmanicidal activity. The *Leishmania* species most used in the assays were: *L. amazonensis*, used in 54 (47.4%) of the studies, *L. infantum*, in 33 (28.9%) of the studies, and *L. major*, in 21 (18.4%) of the studies. Table 13.1 presents the EOs of plant species from 74 genera belonging to 26 families, among which the most frequent were Lamiaceae with 14 genera (18.9%), Asteraceae with 9 genera (12.1%), and Myrtaceae with 8 genera (10.8%).

Of the 114 studies included in the review, 100 (87.7%) performed the chemical characterization of the EOs and 14 (12.3%) did not. Carvacrol was the major constituent most present in the EOs, being reported in 8 studies (7%), followed by thymol, cited in 7 studies (6.1%), and α-pinene and 1,8-cineole cited in 5 studies (4.3%) each.

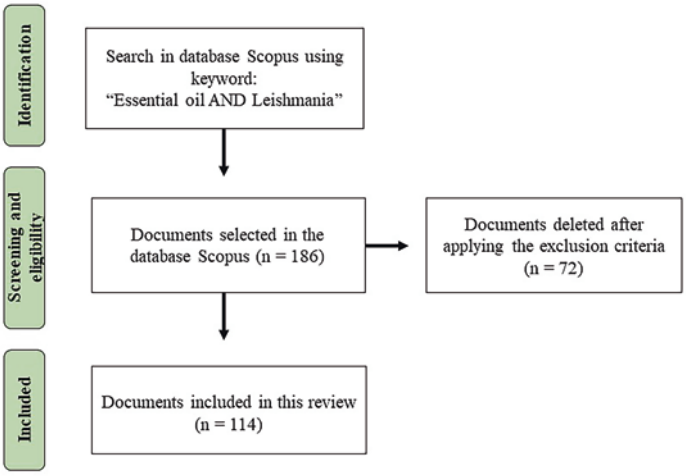

Fig. 13.1 Flowchart of selection of scientific documents included in this review

Table 13.1 Antileishmanial activity of aromatic species

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Própolis tunisiana	Promastigote	*L. major*	5.29 μg/mL	α-pinene (36.7%)	Jihene et al. (2020)
Própolis tunisiana	Promastigote	*L. infantum*	3.67 μg/mL	α-pinene (36.7%)	Jihene et al. (2020)
Própolis tunisiana	Amastigote	*L. major*	7.38 μg/mL	α-pinene (36.7%)	Jihene et al. (2020)
Própolis tunisiana	Amastigote	*L. infantum*	4.96 μg/mL	α-pinene (36.7%)	Jihene et al. (2020)
Amaranthaceae					
Dysphania ambrosioides (L.) Mosyakin & Clemants	Amastigote	*L. amazonensis*	4.9 μg/mL para L. *amazonensis*	–	Machín et al. (2019)
Dysphania ambrosioides (L.) Mosyakin & Clemants	Amastigote	*L. amazonensis*	4.7 μg/mL	Carvacrol (62%)	Monzote et al. (2011)
Dysphania ambrosioides (L.) Mosyakin & Clemants	Promastigote	*L. amazonensis*	2.9 μg/mL	Carvacrol (62%)	Monzote et al. (2011)
Dysphania ambrosioides (L.) Mosyakin & Clemants	Amastigote	*L. amazonensis*	4.6 μg/mL	–	Monzote et al. (2014d)
Dysphania ambrosioides (L.) Mosyakin & Clemants	Promastigote	*L. amazonensis*	3.7 μg/mL	–	Monzote et al. (2014d)
Dysphania ambrosioides (L.) Mosyakin & Clemants	Promastigote	*L. tropica*	1.83 μg/mL	4-careno (56.59%); o-cimeno (41.46%)	Ali et al. (2021)
Anacardiaceae					
Myracrodruon urundeuva (Engl.) Fr. All.	Promastigote	*L. amazonensis*	205 μg/mL	β-myrcene (42.46%); α-myrcene (37.23%)	Carvalho et al. (2017)
Myracrodruon urundeuva (Engl.) Fr. All.	Amastigote	*L. amazonensis*	44.5 μg/mL	β-myrcene (42.46%); α-myrcene (37.23%)	Carvalho et al. (2017)
Pistacia vera L.	Amastigote	*L. tropica*	21.3 μg/mL	Limonene (26.21%)	Mahmoudvand et al. (2015b)
Pistacia lentiscus L.	Promastigote	*L. infantum*	11.28 μg/mL	Myrcene (33.46%)	Bouyahya et al. (2019)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Pistacia lentiscus L.	Promastigote	*L. infantum*	8 μg/mL	α-pinene (20.46%)	Bouyahya et al. (2019)
Annonaceae					
Annona crassiflora Mart.	Promastigote	*L. infantum*	25.97 μg/mL	α-amorphene (43.6%)	Oliani et al. (2013)
Annona coriacea Mart	Promastigote	*L. major*	305.20 μg/mL	Bicyclogermacrene (36%)	Siqueira et al. (2011)
Annona coriacea Mart	Promastigote	*L. infantum*	39.93 μg/mL	Bicyclogermacrene (36%)	Siqueira et al. (2011)
Annona coriacea Mart	Promastigote	*L. brasiliensis*	261.20 μg/mL	Bicyclogermacrene (36%)	Siqueira et al. (2011)
Annona coriacea Mart	Promastigote	*L. amazonensis*	160.20 μg/mL	Bicyclogermacrene (36%)	Siqueira et al. (2011)
Bocageopsis multiflora (Mart.) R.E.Fr.	Promastigote	*L. amazonensis*	14.6 μg/mL	Spathulenol (16.2%)	Oliveira et al. (2014)
Guatteria australis A.St.-Hil.	Promastigote	*L. infantum*	30.71 μg/mL	Germacrene B (50.66%)	Siqueira et al. (2015)
Coriandrum sativum L.	Promastigote	*L. donovani*	26.58 μg/mL	E)-2-undecenal; (E)-2-decenal; (E)-2- Dodecenal	Donega et al. (2014)
Apiaceae					
Ferula galbaniflua Boiss. & Buhse	Promastigote	*L. amazonensis*	95.70 μg/mL	Methyl-8-pimaren-18-oate (41.82%)	Andrade et al. (2016)
Ferula communis L.	Promastigote	*L. major*	0.11 μg/mL	–	Essid et al. (2015)
Ferula communis L.	Promastigote	*L. infantum*	0.05 μg/mL	–	Essid et al. (2015)
Pseudotrachydium kotschyi (Boiss.) Pimenov & Kljuykov	Amastigote	*L. major*	–	Z-α-trans- Bergamotol (23.25%)	Ashrafi et al. (2020b)
Arecaceae					
Scheelea phalerata Mart. ex Spreng	Promastigote	*L. amazonensis*	165.5 μg/mL	Phytol (36.7%)	Oliveira et al. (2020)

Asteraceae					
Artemisia absinthium L.	Promastigote	*L. major*	1.49 μg/mL	Chamazuleno (39.2%)	Mathlouthi et al. (2018)
Artemisia absinthium L.	Amastigote	*L. amazonensis*	13.4 μg/mL	Acetato de trans-sabinil (36.7%)	Monzote et al. (2014a)
Artemisia absinthium L.	Promastigote	*L. amazonensis*	14.4 μg/mL	Acetato de trans-sabinil (36.7%)	Monzote et al. (2014a)
Artemisia absinthium L. (E2)	Promastigote	*L. infantum*	<100 μg/mL	Cis-Epoxyocimene (59.9%)	Bailen et al. (2013)
Artemisia absinthium L. (SNC)	Promastigote	*L. infantum*	<100 μg/mL	–	Bailen et al. (2013)
Artemisia annua L.	Amastigote	*L. donovani*	7.3 μg/mL	Camphor (52.06%)	Islamuddin et al. (2014a)
Artemisia annua L.	Promastigote	*L. donovani*	14.63 μg/mL	Camphor (52.06%)	Islamuddin et al. (2014a)
Artemisia campestris L.	Promastigote	*L. major*	2.20 μg/mL	β-pineno (32%)	Mathlouthi et al. (2018)
Artemisia campestris L.	Promastigote	*L. infantum*	44 μg/mL	*β*-pinene (32.95%)	Aloui et al. (2016)
Artemisia dracunculus L.	Promastigote	*L. tropica*	111 μg/mL	p-allyanisole (67.62%)	Ghanbariasad et al. (2021b)
Artemisia dracunculus L.	Promastigote	*L. major*	114 μg/mL	p-allyanisole (67.62%)	Ghanbariasad et al. (2021b)
Artemisia herba alba Asso	Promastigote	*L. major*	1.20 μg/mL	α-thujone (29.3%)	Mathlouthi et al. (2018)
Artemisia herba alba Asso	Promastigote	*L. infantum*	68 μg/mL	Camphor (36.82%)	Aloui et al. (2016)
Artemisia ludoviciana Nutt.	Promastigote	*L. infantum*	<64 mg/mL	Camphor (40.6%); 1,8-cineole (25.5%)	Baldemir et al. (2018)
Eremanthus erythropappus (DC) McLeisch	Promastigote	*L. amazonensis*	9.53 μg/mL	α-bisabolol (85.98%)	Gomes et al. (2020)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Matricaria chamomilla L.	Promastigote	*L. amazonensis*	3.33 μg/mL	–	Jorjani et al. (2017)
Matricaria chamomilla L.	Amastigote	*L. amazonensis*	14.56 μg/mL	–	Jorjani et al. (2017)
Matricaria chamomilla L.	Promastigote	*L. amazonensis*	60.16 μg/mL	β-farnesene (52.73%)	Andrade et al. (2016)
Matricaria recutita L.	Promastigote	*L. amazonensis*	10.4 μg/mL	–	Hajaji et al. (2018)
Matricaria recutita L.	Promastigote	*L. infantum*	10.8 μg/mL	–	Hajaji et al. (2018)
Melampodium divaricatum (Rich.) DC.	Amastigote	*L. amazonensis*	10.7 μg/mL	E-caryophyllene (56.0%)	Moreira et al. (2019)
Melampodium divaricatum (Rich.) DC.	Promastigote	*L. amazonensis*	24.2 μg/mL	E-caryophyllene (56.0%)	Moreira et al. (2019)
Pluchea carolinensis (Jacq.) G. Don.	Promastigote	*L. amazonensis*	24.7 μg/mL	Selin-11-en-4α-ol (51.0%)	García et al. (2017)
Pluchea carolinensis (Jacq.) G. Don.	Amastigote	*L. amazonensis*	6.2 μg/mL	Selin-11-en-4α-ol (51.0%)	García et al. (2017)
Pulicaria vulgaris Gaertn.	Promastigote	*L. major*	25.64 μg/mL	Thymol (50.22%)	Sharifi-Rad et al. (2018)
Pulicaria vulgaris Gaertn.	Promastigote	*L. infantum*	18.54 μg/mL	Thymol (50.22%)	Sharifi-Rad et al. (2018)
Tagetes lucida Cav.	Promastigote	*L. amazonensis*	118.8 μg/mL	Methyl chavicol (97%)	Monzote et al. (2020b)
Tagetes lucida Cav.	Promastigote	*L. tarentolae*	61.4 μg/mL	Methyl chavicol (97%)	Monzote et al. (2020b)

Vanillosmopsis arborea Baker	Promastigote	*L. amazonensis*	7.35 μg/mL	α-bisabolol (97.9%)	Colares et al. (2013)
Vanillosmopsis arborea Baker	Amastigote	*L. amazonensis*	12.58 μg/mL	α-bisabolol (97.9%)	Colares et al. (2013)
Vernonia brasiliana (L.) Druce	Promastigote	*L. infantum*	39.01 μg/mL	β-cariofileno (21.47%)	Mondego-Oliveira et al. (2021)
Vernonia polyanthes Less	Promastigote	*L. infantum*	19.4 μg/mL para	Myrcene (34.3%)	Moreira et al. (2017).
Bixaceae					
Bixa orellana L.	Amastigote	*L. amazonensis*	8.5 μg/mL	–	Machín et al. (2019)
Bixa orellana L.	Amastigote	*L. amazonensis*	8.5 μg/mL	Ishwarane (18.6%)	Monzote et al. (2014c)
Bixa orellana L. (Nanocomplexo)	Amastigote	*L. amazonensis*	15.4 μg/mL	–	Machín et al. (2019)
Burseraceae					
Bursera graveolens Triana & Planch.	Amastigote	*L. amazonensis*	36.7 μg/mL	Limonene (26.5%)	Monzote et al. (2012).
Protium heptaphyllum (Aubl.) Marchand		*L. amazonensis*	9.02 μg/mL	–	Cabral et al. (2021)
Protium ovatum Engl.	Promastigote	*L. amazonensis*	2.28 μg/mL	–	Estevam et al. (2017)
Canellaceae					
Cinnamodendron dinisii Schwacke	Promastigote	*L. amazonensis*	54.05 μg/mL	α-pinene (35.41%)	Andrade et al. (2016)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Euphorbiaceae					
Croton nepetifolius Baill.	Promastigote	*L. amazonensis*	9.87 μg/mL	Methyl eugenol (33.89%)	Morais et al. (2019).
Croton rhamnifolioides Pax & K. Hoffm.	Promastigote	*L. braziliensis*	127.43 μg/mL	–	Alcântara et al. (2021)
Croton rhamnifolioides Pax & K. Hoffm.	Promastigote	*L. infantum*	111.84 μg/mL	–	Alcântara et al. (2021)
Croton linearis Jacq.	Promastigote	*L. amazonensis*	20.0 μg/mL	–	Díaz et al. (2018)
Croton linearis Jacq	Amastigote	*L. amazonensis*	13.8 μg/mL	–	Díaz et al. (2018)
Fabaceae					
Copaifera sp.	Promastigote	*L. amazonensis*	18 μg/mL	–	Moraes et al. (2018).
Copaifera sp.	Promastigote	*L. infantum*	16 μg/mL	–	Moraes et al. (2018).
Copaifera guianensis Desf.	Promastigote	*L. amazonensis*	590 μg/mL	–	Moraes et al. (2018).
Copaifera guianensis Desf.	Promastigote	*L. infantum*	366 μg/mL	–	Moraes et al. (2018).
Copaifera reticulata Ducke	Amastigote	*L. infantum*	0.52 μg/mL	β-linalool (73.21%)	Rottini et al. (2019)
Copaifera reticulata Ducke	Promastigote	*L. infantum*	7.88 μg/mL	β-linalool (73.21%)	Rottini et al. (2019)
Geraniaceae					
Pelargonium graveolens L'Hér.	Promastigote	*L. major*	0.28 μg/mL	Citronellol (24.75%)	Essid et al. (2015)
Pelargonium graveolens L'Hér.	Promastigote	*L. infantum*	0.11 μg/mL	Citronellol (24.75%)	Essid et al. (2015)

Lamiaceae					
Elsholtzia ciliata (Thunb.) Hyl.	Promastigote	*L. mexicana*	8.49 nl/mL	Geranial (23.4%)	Le et al. (2017)
Lavandula luisieri (Lavandula stoechas var. *luisieri)*	Promastigote	*L. infantum*	63 μg/mL	Necrodane derivatives (36%)	Machado et al. (2019)
Lavandula luisieri (Lavandula stoechas var. *luisieri)*	Promastigote	*L. tropica*	38 μg/mL	Necrodane derivatives (36%)	Machado et al. (2019)
Lavandula luisieri	Promastigote	*L. major*	31 μg/mL	Necrodane derivatives (36%)	Machado et al. (2019)
Lavandula stoechas L.	Promastigote	*L. major*	0.9 μg/mL	Fenchone (31.81%); camphor (29.60%)	Bouyahya et al. (2017b)
Mentha australis R.Br.	Promastigote	*L. donovani*	3.7 μg/mL	β-linalool (22.9%)	Ibrahim et al. (2017)
Melissa officinalis L.	Promastigote	*L. braziliensis*	<125 μg/mL	Geranial (35.69%); Z citral (25.51%)	Costa et al. (2016)
Mentha pulegium L.	Promastigote	*L. major*	1.3 μg/mL	Menthone (21.1%); pulegone (40.9%)	Bouyahya et al. (2017c)
Nepeta curvidens Boiss. & Balansa	Amastigote	*L. major*	71.02 μg/mL	–	Ashrafi et al. (2020a)
Origanum compactum Benth.	Promastigote	*L. major*	0.13 μg/mL	Carvacrol (43.5%)	Bouyahya et al. (2017a)
Origanum compactum Benth.	Promastigote	*L. infantum*	0.02 μg/mL	Carvacrol (43.5%)	Bouyahya et al. (2017a)
Origanum compactum Benth.	Promastigote	*L. tropica*	0.22 μg/mL	Carvacrol (43.5%)	Bouyahya et al. (2017a)
Ocimum canum Sims	Promastigote	*L. amazonensis*	17.4 μg/mL	Thymol (42.15%); p-cymene (21.17%)	Silva et al. (2018)
Ocimum canum Sims	Amastigote	*L. amazonensis*	13.1 μg/mL	Thymol (42.15%); p-cymene (21.17%)	Silva et al. (2018)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Ocimum gratissimum L.	Promastigote	*L. mexicana*	4.85 nl/mL	Eugenol (86.5%)	Le et al. (2017)
Origanum onites L.	Promastigote	*L. donovani*	17.8 μg/mL	Carvacrol (70.6%)	Tasdemir et al. (2019)
Plectranthus amboinicus (Lour.) Spreng	Promastigote	*L. amazonensis*	58.2 μg/mL	Carvacrol (71%)	Monzote et al. (2020c)
Rosmarinus officinalis L.	Promastigote	*L. infantum*	1.2 μg/mL	1,8-Cineole (23.6%)	Bouyahya et al. (2017c)
Satureja khuzestanica Jamzad	Amastigote	*L. major*	–	–	Kheirandish et al. (2011)
Tetradenia riparia (Hochst.) Codd	Promastigote	*L. amazonensis*	15.67 ng/mL	–	Cardoso et al. (2015)
Tetradenia riparia (Hochst.) Codd	Amastigote	*L. amazonensis*	15.67 ng/mL	–	Cardoso et al. (2015)
Tetradenia riparia (Hochst.) Codd	Promastigote	*L. amazonensis*	0.03 μg/mL	–	Demarchi et al. (2016)
Tetradenia riparia (Hochst.) Codd	Amastigote	*L. amazonensis*	0.5 μg/mL	–	Demarchi et al. (2016)
Teucrium polium Decne.	Promastigote	*L. major*	0.15 μg/mL	Carvacrol (56.06%)	Essid et al. (2015)
Teucrium polium Decne.	Promastigote	*L. infantum*	0.09 μg/mL	Carvacrol (56.06%)	Essid et al. (2015)
Teucrium polium Decne.	Promastigote	*L. donovani*	2.3 μg/mL	–	Ibrahim et al. (2017)
Thymus capitellatus Hoffmanns. & Link	Promastigote	*L. infantum*	37 μg/mL	1,8-cineol (58.6%)	Machado et al. (2014)
Thymus capitellatus Hoffmanns. & Link	Promastigote	*L. tropica*	35 μg/mL	1,8-cineol (58.6%)	Machado et al. (2014)
Thymus capitellatus Hoffmanns. & Link	Promastigote	*L. major*	62 μg/mL	1,8-cineol (58.6%)	Machado et al. (2014)
Thymus hirtus sp. *algeriensis*	Promastigote	*L. major* e	0.43 μg/mL	–	Ahmed et al. (2011)

Thymus hirtus sp. *algeriensis*	Promastigote	*L. infantum*	0.25 μg/mL	–	Ahmed et al. (2011)
Zataria multiflora Boiss.	Promastigote	*L. tropica*	3.2 μL/mL	Thymol (41.81%); carvacrol (28.85%)	Dezaki et al. (2016)
Zataria multiflora Boiss.	Amastigote	*L. tropica*	8.3 μL/mL	Thymol (41.81%); carvacrol (28.85%)	Dezaki et al. (2016)
Lauraceae					
Cinnamomum cassia (L.) J. Presl	Promastigote	*L. mexicana*	2.92 nl/mL	Trans-Cinnamaldehyde (83.6%)	Le et al. (2017)
Cinnamomum verum J.Presl	Promastigote	*L. mexicana*	21 μg/mL	Cinnamaldehyde (73.3%)	Andrade-Ochoa et al. (2021)
Cinnamomum zeylanicum Blume	Promastigote	*L. tropica*	7.56 μg/mL	Cinnamaldehyde (62.04%)	Ghanbariasad et al. (2021a)
Cinnamomum zeylanicum Blume	Promastigote	*L. major*	16.53 μg/mL	Cinnamaldehyde (62.04%)	Ghanbariasad et al. (2021c)
Cryptocarya aschersoniana Mez	Promastigote	*L. amazonensis*	4.46 μg/mL	Limonene (42.3%)	Andrade et al. (2018a)
Endlicheria bracteolata (Meisn.)	Amastigote	*L. amazonensis*	3.54 μg/mL	Guaiol (46.4%)	Sales et al. (2018)
Endlicheria bracteolata (Meisn.)	Promastigote	*L. amazonensis*	7.94 μg/mL	Guaiol (46.4%)	Sales et al. (2018)
Nectandra gardneri Meisn.	Amastigote	*L. infantum*	2.7 μg/mL	Intermediol (58.2%)	Bosquiroli et al. (2017)
Nectandra gardneri Meisn.	Amastigote	*L. amazonensis*	2.1 μg/mL	Intermediol (58.2%)	Bosquiroli et al. (2017)
Nectandra hihua (Ruiz & Pav.) Rohwer	Amastigote	*L. infantum*	0.2 μg/mL	Bicyclogermacrene (28.1%)	Bosquiroli et al. (2017)
Nectandra hihua (Ruiz & Pav.) Rohwer	Amastigote	*L. amazonensis*	0.2 μg/mL	Bicyclogermacrene (28.1%)	Bosquiroli et al. (2017)
Nectandra megapotamica (Spreng.) Mez	Promastigote	*L. amazonensis*	6.66 μg/mL	–	Almeida et al. (2020)
Ocotea dispersa (Nees & Mart.) Mez	Promastigote	*L. amazonensis*	4.67 μg/mL	α-eudesmol (20.9%)	Alcoba et al. (2018)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Ocotea odorífera (Vell.) Rohwer	Promastigote	*L. amazonensis*	11.67 μg/mL	Safrole (36.3%)	Alcoba et al. (2018)
Meliaceae					
Guarea macrophylla Vahl	Promastigote	*L. amazonensis*	11.8 μg/mL	–	Oliveira et al. (2019)
Myrtaceae					
Campomanesia xanthocarpa (Mart.) O.Berg	Promastigote	*L. amazonensis*	70 μg/mL	–	Ferreira et al. (2020)
Campomanesia xanthocarpa (Mart.) O.Berg	Amastigote	*L. amazonensis*	6 μg/mL	–	
Eugenia gracillima Kiaersk.	Promastigote	*L. braziliensis*	74.64 μg/mL	–	Sampaio et al. (2021)
Eugenia gracillima Kiaersk.	Promastigote	*L. infantum*	80.4 μg/mL	–	Sampaio et al. (2021)
Eugenia piauhiensis Vellaff.	Amastigote	*L. amazonensis*	4.59 μg/mL	γ-Elemene (23.5%)	Nunes et al. (2021)
Eugenia piauhiensis Vellaff.	Promastigote	*L. amazonensis*	6.43 μg/mL	γ-Elemene (23.5%)	Nunes et al. (2021)
Eugenia pitanga (O.Berg) Nied.	Promastigote	*L. amazonensis*	6.10 μg/mL	–	Kauffmann et al. (2017)
Myrcia ovata Cambess.	Promastigote	*L. amazonensis*	8.69 μg/mL	Geranial (52.6%); Neral (37.1%)	Gomes et al. (2020)
Myrciaria plinioides D.Legrand	Promastigote	*L. amazonensis*	14.16 μg/mL	Spathulenol (21.12%)	Kauffmann et al. (2019)
Myrciaria plinioides D.Legrand	Promastigote	*L. infantum*	101.50 μg/mL	Spathulenol (21.12%)	Kauffmann et al. (2019)

Myrtus communis L.	Promastigote	*L. tropica*	8.4 μg/mL	α-pinene (24.7%)	Mahmoudvand et al. (2015a)
Psidium myrsinites DC.	Promastigote	*L. braziliensis*	52.2 μg/mL	–	Vandesmet et al. (2020)
Syzygium aromaticum (L.) Merr. & L.M.Perry	Promastigote	*L. major*	654.76 μg/mL	Eugenol (65.41%)	Moemenbellah-Fard et al. (2020)
Syzygium aromaticum (L.) Merr. & L.M.Perry	Promastigote	*L. tropica*	180.24 μg/mL	Eugenol (65.41%)	Moemenbellah-Fard et al. (2020)
Syzygium aromaticum (L.) Merr. & L.M.Perry	Promastigote	*L. amazonensis*	60.0 μg/mL	Eugenol (59.75%); eugenyl Acetate (29.24%)	Islamuddin et al. (2014b)
Syzygium aromaticum (L.) Merr. & L.M.Perry	Amastigote	*L. amazonensis*	43.9 μg/mL	Eugenol (59.75%); eugenyl Acetate (29.24%)	Rodrigues et al. (2015)
Syzygium cumini (L.) Skeels	Promastigote	*L. amazonensis*	60 mg/L	α-pinene (31.85%); (Z)-b-ocimene (28.98%)	Dias et al. (2013)
Piperaceae					
Piper aduncum L.	Promastigote	*L. amazonensis*	25.9 μg/mL	Bicyclogermacrene (20.9%)	Bernuci et al. (2016)
Piper aduncum L.	Amastigote	*L. amazonensis*	36.2 μg/mL	Bicyclogermacrene (20.9%)	Bernuci et al. (2016)
Piper aduncum L.	Promastigote	*L. braziliensis*	77.9 μg/mL	–	Ceole et al. (2017)
Piper aduncum var. *ossanum*	Promastigote	*L. amazonensis*	19.3 μg/mL	Piperitone (20.07%)	Gutiérrez et al. (2016)
Piper aduncum var. *ossanum*	Promastigote	*L. infantum*	32.5 μg/mL	Piperitone (20.07%)	Gutiérrez et al. (2016)
Piper angustifolium Ruiz & Pav.	Amastigote	*L. infantum*	1.43 μg/mL	Spathulenol (23.8%)	Bosquiroli et al. (2015)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Piper claussenianum (Miq.) C.DC.	Promastigote	*L. amazonensis*	21.3 μg/mL	(E)-nerolidol (83.29%)	Marques et al. (2011)
Piper cernuum Vell.	Amastigote	*L. amazonensis*	–	β-elemene (30.0%)	Capello et al. (2015)
Piper demeraranum (Miq.) C.DC.	Promastigote	*L. amazonensis*	86 μg/mL	β-elemene (33.1%)	Carmo et al. (2012)
Piper demeraranum (Miq.) C.DC.	Amastigote	*L. amazonensis*	78 μg/mL	β-elemene (33.1%)	Carmo et al. (2012)
Piper demeraranum (Miq.) C.DC.	Promastigote	*L. guyanensis*	22.7 μg/mL	β-elemene (33.1%)	Carmo et al. (2012)
Piper demeraranum (Miq.) C.DC.	Amastigote	*L. guyanensis*	22.7 μg/mL	β-elemene (33.1%)	Carmo et al. (2012)
Piper diospyrifolium Kunth	Promastigote	*L. amazonensis*	13.5 μg/mL	–	Bernuci et al. (2016)
Piper diospyrifolium Kunth	Amastigote	*L. amazonensis*	76.1 μg/mL	–	Bernuci et al. (2016)
Piper duckei C.DC.	Promastigote	*L. amazonensis*	46 μg/mL	Trans-caryophyllene (27.1%)	Carmo et al. (2012)
Piper duckei C.DC.	Amastigote	*L. amazonensis*	42.4 μg/mL	Trans-caryophyllene (27.1%)	Carmo et al. (2012)
Piper duckei C.DC.	Promastigote	*L. guyanensis*	15.2 μg/mL	Trans-caryophyllene (27.1%)	Carmo et al. (2012)
Piper hispidum Sw.	Amastigote	*L. amazonensis*	3.4 μg/mL	–	Houël et al. (2015)
Piper tuberculatum Jacq	Promastigote	*L. brasiliensis*	143.59 μg/mL	β-pinene (27.74%)	Sanchez-Suarez et al. (2013)
Piper tuberculatum Jacq	Promastigote	*L. infantum*	133.97 μg/mL	β-pinene (27.74%)	Sanchez-Suarez et al. (2013)

Piper var. *brachypodom* (Benth.) C. DC.	Promastigote	*L. infantum*	23.68 μg/mL	trans-ß-caryophyllene (20.2%)	Leal et al. (2013)
Piper var. *brachypodom* (Benth.) C. DC.	Amastigote	*L. infantum*	62.82 μg/mL	Trans-ß-caryophyllene (20.2%)	Leal et al. (2013)
Piper marginatum Jacq.	Amastigote	*L. amazonensis*	0.58 μg/mL	3,4-methylenedioxypropiophenone (22.9%)	Macêdo et al. (2020)
Piper marginatum Jacq.	Promastigote	*L. amazonensis*	7.9 μg/mL	3,4-methylenedioxypropiophenone (22.9%)	Macêdo et al. (2020)
Poaceae					
Cymbopogon citratus (DC.) Stapf	Promastigote	*L. infantum*	25 μg/mL	Geranial (45.7%); Neral (32.5%)	Machado et al. (2012a)
Cymbopogon citratus (DC.) Stapf	Promastigote	*L. tropica*	52 μg/mL	Geranial (45.7%); Neral (32.5%)	Machado et al. (2012a)
Cymbopogon citratus (DC.) Stapf	Promastigote	*L. major*	38 μg/mL	Geranial (45.7%); Neral (32.5%)	Machado et al. (2012a)
Ranunculaceae					
Nigella sativa L.	Promastigote	*L. infantum*	62.1 μg/mL	Thymoquinone (42.4%)	Mahmoudvand et al. (2015a)
Nigella sativa L.	Promastigote	*L. tropica*	53.3 μg/mL	Thymoquinone (42.4%)	Mahmoudvand et al. (2015a)
Nigella sativa L.	Promastigote	*L. tropica*	–	–	Abamor and Allahverdiyev 2016
Nigella sativa L.	Amastigote	*L. tropica*	–	–	Abamor and Allahverdiyev 2016
Rosaceae					
Agrimonia pilosa Ledeb	Promastigote	*L. donovani*	<100 μg/mL	–	Dhami et al. (2021)
Agrimonia pilosa Ledeb	Amastigote	*L. donovani*	<100 μg/mL	–	Dhami et al. (2021)

(continued)

Table 13.1 (continued)

Family/Species	Evolutionary form	Species	IC_{50}	Majority constituents	Reference
Rubiaceae					
Mitracarpus frigidus (Willd. ex Roem. & Schult.) K.Schum.	Promastigote	*L. major*	47.2 μg/mL	Linalool (29.29%)	Fabri et al. (2012)
Mitracarpus frigidus (Willd. ex Roem. & Schult.) K.Schum.	Promastigote	*L. amazonensis*	89.7 μg/mL	Linalool (29.29%)	Fabri et al. (2012)
Rutaceae					
Citrus limon L.	Amastigote	*L. major*	4.2 μg/mL	Neryl acetate (29.5%)	Maaroufi et al. (2021)
Citrus sinensis (L.) Osbeck	Promastigote	*L. tropica*	151.13 μg/mL	Limonene (71.264%)	Ghanbariasad et al. (2021a)
Citrus sinensis (L.) Osbeck	Promastigote	*L. major*	108.31 μg/mL	Limonene (71.264%)	Ghanbariasad et al. (2021a)
Haplophyllum tuberculatum A. Juss.	Promastigote	*L. mexicana*	6.48 μg/mL	–	Hamdi et al. (2018)
Ruta chalepensis L.	Promastigote	*L. major*	1.13 μg/mL	2-undecanone (84.28%)	Ahmed et al. (2011)
Ruta chalepensis L.	Promastigote	*L. infantum*	1.13 μg/mL	2-undecanone (84.28%)	Ahmed et al. (2011)
Salicaceae					
Casearia sylvestris SW.	Amastigote	*L. amazonensis*	14.0 μg/mL	E-caryophyllene (22.2%)	Moreira et al. (2019)
Casearia sylvestris SW.	Promastigote	*L. amazonensis*	29.8 μg/mL	E-caryophyllene (22.2%)	Moreira et al. (2019)
Verbenaceae					
Aloysia gratissima (Gillies & Hook.) Tronc.	Promastigote	*L. amazonensis*	25 μg/mL	–	Garcia et al. (2018)
Aloysia gratissima (Gillies & Hook.) Tronc.	Amastigote	*L. amazonensis*	0.16 μg/mL	–	Garcia et al. (2018)

Lantana camara L.	Promastigote	*L. braziliensis*	72.31 μg/mL	(E)-caryophyllene (23.75%)	Barros et al. (2016)
Lantana camara L.	Promastigote	*L. infantum*	0.25 μg/mL para *L. amazonensis*	Germacrene D (24.90%)	Machado et al. (2012b)
Lantana camara L.	Promastigote	*L. amazonensis*	18 μg/mL para *L. infantum*	Germacrene D (24.90%)	Machado et al. (2012b)
Lippia berlandieri Schauer	Promastigote	*L. mexicana*	59 μg/mL	Thymol (58.3%); p-Cymene (24.6%)	Andrade-Ochoa et al. (2021)
Lippia gracilis Schauer	Promastigote	*L. infantum*	86.32 μg/mL	Thymol (61.84%)	Melo et al. (2013)
Lippia sidoides Cham.	Amastigote	*L. amazonensis*	34.4 μg/mL	Thymol (78.37%)	Medeiros et al. (2011)
Lippia sidoides Cham.	Promastigote	*L. amazonensis*	44.3 μg/mL	Thymol (78.37%)	Medeiros et al. (2011)
Lippia sidoides Cham.	Promastigote	*L. infantum*	54.8 μg/mL	Carvacrol (43.7%)	Farias-Junior et al. (2012)
Lippia origanoides Kunth	Promastigote	*L. brasiliensis*	0.39 μg/mL	–	Neira et al. (2018)
Zingiberaceae					
Alpinia speciosa K. Schum	Promastigote	*L. brasiliensis*	67.18 μg/mL	1,8-cineole (28.46%)	Pereira et al. (2018)
Curcuma longa L.	Amastigote	*L. amazonensis*	63.3 μg/mL	Turmerone (55.43%)	Teles et al. (2019)
Zingiber zerumbet (L.) Sm.	Promastigote	*L. mexicana*	3.34 nl/mL	Zerumbone (60.3%)	Le et al. (2017)
Amomum aromaticum Roxb.	Promastigote	*L. mexicana*	9.25 nl/mL	Eucalyptol (55.2%)	Le et al. (2017)
Zygophyllaceae					
Bulnesia sarmientoi Lorentz ex Griseb.	Promastigote	*L. amazonensis*	85.56 μg/mL	Guaiol (48.29%)	Andrade et al. (2016)

Seventeen articles (14.9%) performed tests to verify the possible mechanism of action of the EOs, while 97 (85.1%) did not. In this sense, among the studies that investigated the mechanism of action, the ones by Demarchi et al. (2015) and Demarchi et al. (2016) with the EO of *Tetradenia riparia* stood out with the best result in terms of IC_{50} (0.03 μg/ml). The leishmanicidal potential of *T. riparia* EO against *L. amazonensis* was explained by the oil's ability to modify the ultrastructure of promastigotes, suggesting an autophagic process with chromatin condensation; presence of blebbings and nuclear fragmentation; decreased macrophage infection rate by amastigotes; and, finally, inhibition of granulocyte and macrophage colony-stimulating factor, interleukin-4 (IL-4), IL-10 and tumor necrosis factor. Other EOs are also noteworthy for their ability to inhibit parasites at low concentrations, such as those from *Origanum compactum* (IC_{50} = 0.02 μg/mL), *Ferula communis* (IC_{50} = 0.05 μg/mL), and *Teucrium polium* (IC_{50} = 0.09 μg/mL) against *L. infantum* isolates.

13.4 Discussion

13.4.1 Essential Oils Against Leishmania spp.

The genus *Leishmania* is a group of flagellated parasites comprising more than 20 different species distributed in the subgenus *Leishmania* or *Viannia*, whose main vectors are phlebotomine sandflies of the genus *Lutzomyia* and *Phlebotomus* (Espinosa et al. 2018). Members of the genus *Leishmania* differentiate from proliferative promastigotes in the insect vector gut into infective metacyclic promastigotes in the foregut of the insect. The parasites are inoculated by the vector as flagellated promastigotes into the mammalian host, where they infect macrophages, differentiating into amastigote forms (Rocha et al. 2005).

Leishmania parasites can be divided according to their clinical forms and manifestations, geographic distribution, and reservoir. *Leishmania (L.) amazonensis*, *L. mexicana L, L. (L.) tropica*, and *L. (V.) guyanensis* are more prevalent in South America and are characterized by causing multiple or individual ulcerative lesions, a condition called cutaneous leishmaniasis. In addition to *L. (V.) braziliensis*, which can cause mucocutaneous changes, *L. infantum* and *L. donovani* cause the most serious conditions called visceral leishmaniasis, which include, but are not limited to persistent fever, splenomegaly, and weight loss (Burza et al. 2018).

The main anti-*Leishmania* therapeutic methods involve the use of pentavalent antimonials, amphotericin B, paromomycin, pentamidine, and miltefosine; however, there is great resistance to treatment adherence due to their high toxicity and side effects, in addition to the financial impact in more poor regions (Roatt et al. 2020). There is also concern about the development of resistant strains and variable response to treatment depending on the parasite species. In Brazil, strains of *L. infantum* resistant to miltefosine have been isolated in patients whose treatment

was unsuccessful. According to Roatt et al. (2020), this finding suggests a natural resistance to this drug because ince it had not yet been used in the country (Carnielli et al. 2019).

The exploration of the plant kingdom is one of the only options for the development of therapeutic agents with high safety and cost-benefit profile for various health problems, as highlighted by Bekhit et al. (2018). The investigation of new compounds that can be used in the treatment of leishmaniasis begins with ethnobotanical studies, which provide information about the medicinal properties of various plant species based on the knowledge disseminated in traditional communities.

Ethnobotanical studies and the investigation of the therapeutic potential of plants make it possible to track new bioactive molecules with the potential to become new drugs in the future. Passero et al. (2021) list 216 species distributed in 76 genera that present contributions to the experimental treatment of leishmaniasis, opening a wide range of options for investigations in the field. A review published by Rocha et al. (2005) found about 239 chemically defined natural molecules reported in the literature which were evaluated for anti-*Leishmania* activity, including alkaloids, terpenes, various lactones, flavonoids, diterpenes, steroids, lipids, carbohydrates, proteins, coumarins, phenylpropanoids, and depsides. Recently, a review published by Fampa et al. (2021) highlighted about 30 volatile compounds that were also evaluated for their anti-*Leishmania* activity.

13.4.2 Terpenes

According to the data obtained, analyses show that, among the different compounds that constitute EOs, terpenes are the most abundant, present both as sesquiterpenes and monoterpenes. The anti-*Leishmania* activity of compounds present in EOs can be attributed to their lipophilic character. Several studies indicate that these substances act by breaking the microbial cytoplasmic membrane, making it permeable, affecting polarization and compromising biological barriers and the enzyme matrix (Cristani et al. 2007).

The EO of *Myrciaria plinioides* leaves was effective against *L. amazonensis* promastigotes and presented an IC_{50} value of 14.16 ± 7.40 μg/mL; however, the activity against *L. infantum* promastigotes was less pronounced, with an IC_{50} value of 101.50 ± 5.78 μg/ml (Kauffmann et al. 2019). The anti-*Leishmania* activity was attributed to the presence of the sesquiterpenes spathulenol **(1)** and caryophyllene oxide **(2)**, which represent 36.32% of the total components that can cause alterations in the mitochondrial membrane potential, in addition to modification of the redox index, inhibition of cellular isoprenoid biosynthesis, and changes in the plasma membrane (Santos et al. 2008; Rodrigues et al. 2013; Monzote et al. 2014c).

The EO of *Lantana camara* was able to cause 100% inhibition of proliferation of *L. amazonensis* at concentrations above 3 μg/mL, and about 90% inhibition in *L. chagasi* at the concentration of 250 μg/mL (Machado et al. 2012b). The presence of germacrene-D **(3)** in the composition of the EO was considered to be responsible

for the inhibitory effect on the growth of promastigote cultures. This hypothesis is based on the activity of amphotericin B, which is able to act as an antifungal and antiparasitic agent, as suggested by tests in germacrene-D **(3)**. It is noteworthy that Biavatti et al. (2001) observed a toxic effect of the EO in tests using brine shrimp and mammalian cells *in vitro*. However, the authors mentioned that this effect was not related to the presence of germacrene-D **(3)**, as it did not present a toxic effect in the same models.

Another terpene with anti-*Leishmania* activity widely cited in the literature is pinene **(4,10)**. More than 40 components were found through gas chromatography analysis in the EO of propolis, with 36.17% of α-pinene **(4)**. In *in vitro* tests, pinene **(4,10)** was effective against the promastigotes and amastigotes of *L. major* and *L. infantum*, with IC_{50} of 5.29 μg/mL and 3.67 μg/mL for promastigotes, and 7.38 μg/mL and 4.96 μg/ml for amastigotes of *L. major* and *L. infantum*, respectively. Furthermore, the EO exhibited synergistic activity with amphotericin B, inhibiting the growth of *Leishmania* by more than 98%. Although the activity was attributed to its major compound, the authors did not rule out a synergy of pinene **(4,10)** with the less expressive components present in the EO (Jihene et al. 2020).

In tests performed by Dias et al. (2013), the EO of *Syzygium cumini* showed good activity against the promastigote forms of *L. amazonensis*. At all concentrations and time points analyzed, significantly higher mortality was observed in the treatment than in the control groups, leading to the conclusion that *S. cumini* EO has leishmanicidal rather than leishmanistatic activity. The greatest efficacy was seen within 24 hours of exposure, with an IC_{50} of 36 mg/L. Although the author did not perform specific tests to determine the mechanisms of action through which the EO acts, leishmanicidal activity was attributed to the lipophilic characteristic of the EO, mentioned above. With 31.85% of α-pinene **(4)** in its composition, its action can be compared to that of the EO of *Cinnamodendron dinisii*, which has 35.41% α-pinene **(4)** (Andrade et al. 2016). Although *C. dinisii* EO has a higher concentration of pinene **(4,10)** in its composition, its activity was lower than that of *S. cumini* EO. It is possible that the minor compounds in these species interfere in the action of pinene **(4,10)**.

Bouyahya et al. (2019) tested the EO of leaves and fruits of *Pistacia lentiscus*, obtaining an IC_{50} of 11.28 and 8 μg/mL, respectively, against *L. infantum*, 17.52 and 21.42 μg/mL against *L. major*, and 23.5 and 26.2 μg/mL against *L. tropica*. Both EOs presented better results than the standard drug glucantime and although they were obtained from *P. lentiscus*, both presented major compounds at different concentrations. In the EO of the leaves, was in higher concentration, 33.46%, while α-pinene **(4)** represented only 19.20%. The EO of the fruits presented 20.46% of α-pinene **(4)**, and the second compound with the highest concentration was limonene **(5)**, corresponding to 18.26%. This shows that the composition of EO can change according to the part of the plant from which it is extracted.

It is known that besides varying according to the part of the plant from which it is extracted, the composition of the EO can be altered by environmental factors such as climate, time of collection, and geographic location (Do Carmo et al. 2012; Essid et al. 2015; Bouyahya et al. 2019). Variability is also present in plants of same genus

but different species. This is the case of *Artimisia* plants studied by Mathlouthi et al. (2018). In their tests, they showed a remarkable anti-*Leishmania* activity, with an IC_{50} of 2.20 μg/mL and 1.20 μg/mL for *Artemisia campestres* and *Artemisia herba-alba*, respectively, both against the promastigote forms of *L. major*. *Artemisia herba-alba* had β-thujone **(8)** (29.4%) and 1,8-cineole **(9)** (14.8%), with only a small fraction of β-pinene **(10)** (2.3%), while *A. campestres* had β-pinene **(10)** (32%) and limonene **(5)** (17.3%), but β-thujone **(8)** was absent.

Although many EOs have shown better results than the isolated compounds, several factors may be involved in these processes. In a study by Do Carmo et al. (2012), the EO of *Piper duckei* showed a lower result than its major compound, trans-caryophyllene, against *L. amazonensis* promastigotes. The IC_{50} was 46 μg/mL for the EO, and 96 μg/mL for the isolated compound. The authors reported that, during the experiments, it was possible to observe that the purity of trans-caryophyllene is an important factor for the activity against *L. amazonensis*. The oxidation of trans-caryophyllene to its corresponding oxides affects the results; depending on the level of oxidation, activity may not be observed. Another plant of the *Piper* genus, *Piper cernuum* Vell, also had caryophyllene **(11)** in its composition (16%). In *in vitro* tests with macrophages infected with *L. amazonensis*, the isolated compound reached greater efficiency in reducing parasite infection in macrophages at concentrations of 2 and 10 μg/mL, leading to infection rates of 105 ± 16 and 101 ± 7, respectively, both lower than values obtained with amphotericin B (34 ± 5 at 0.1 μg/mL), but superior to those obtained with the EO (131 ± 15 at 2 μg/mL and 115 ± 13 at 10 μg/mL). According to Capello et al. (2015), the effect of the EO may be associated with bioactive sesquiterpenes present in its composition.

In a research carried out by Essid et al. (2015), compounds of the EOs extracted from *F. communis*, *T. polium*, and *Pelargonium graveolens* exhibited strong inhibitory activity against the growth of promastigote forms of *L. major* and *L. infantum*, with IC_{50} values <1 μg/mL. Their main constituents were β-caryophyllene **(11)**, carvacrol **(12)** and citronellol **(13)** respectively. In tests with the isolated compounds, β-caryophyllene **(11)** was the most active, with an IC_{50} of 1.06 ± 0.37 μg/mL for *L. infantum* and 1.33 ± 0.52 μg/mL for *L. major*. Carvacrol **(12)** had an IC_{50} of 7.35 ± 1.78 g/mL for *L. infantum* and 9.15 ± 0.12 g/mL for *L. major*. Very low activity was recorded for citronellol **(13)**. It is interesting to note that the isolated compounds showed lower activity than the EO.

According to Carvalho et al. (2017), EOs are more effective than their individual chemical constituents. Their bioactivity depends on the additive and synergistic action of the components. The EO of *Cymbopogon citratus* and its major constituents citral **(14)** (neral **(15)** 40% + geranial **(16)** 60%) and myrcene **(6,7)** were tested against *L. infantum* by Machado et al. (2012a), resulting in IC_{50} values of 25 μg/mL for the EO, 42 μg/mL for citral **(14)**, and 164 μg/mL for myrcene **(6,7)**, thus showing the best result for the EO. In a work carried out by Moreira et al. (2017), the EO of *Vernonia polyanthes* Less presented an IC_{50} of 19.4 μg/mL against *L. infantum*, lower than the IC_{50} of zerumbone **(17)** (9 μg/mL), a monoterpene present in the EO.

On the other hand, in the work by Leal et al. (2013), the EOs of *Piper brachypodom* and *Piper var. brachypodom* presented trans-ß-caryophyllene **(11)** as the major

component (20.2%). The results showed that the EOs were more active against *L. infantum* promastigotes (IC_{50} 23.43 and 23.68 μg/mL, respectively). However, none of these EOs was active against the intracellular forms of this protozoan. Trans-ß-caryophyllene **(11)** had an IC_{50} of 24.02 μg/mL against *L. infantum* promastigotes, a result slightly lower than that obtained for the EOs, but it was active against amastigote forms, with an IC_{50} of 53.39 μg/mL. The author stated that it is much more difficult for components to reach intracellular forms because they need to penetrate barriers and reach the place where the parasite is alive, as opposed to free forms in whose case the product can act directly on the parasite. Considering the similarity of the results, it is possible to say that the action of *Piper* EOs is due to its major constituent, and that the constituents with lower expression possibly acted negatively, preventing the action of the EOs in the intracellular forms of *L. infantum*.

According to Cristani et al. (2007), the activity of monoterpernes such as carvacrol **(12)** and thymol **(18)** results from the disturbance of the lipid fraction of the plasma membrane of microorganisms, as bacteria. Other studies point to the same type of interaction in parasites and claim that terpenes are responsible for the hydrophobic characteristic of EOs, allowing their diffusion across the cell membrane of parasites such as *Leishmania* and affecting intracellular metabolic pathways and organelles (Andrade et al. 2016).

In a work carried out by de Medeiros et al. (2011), the incubation of *L. amazonensis* promastigotes with *Lippia sidoides* EO and its main constituent thymol **(18)** efficiently inhibited the growth of the parasite. IC_{50}/48 h values were 44.38 and 19.47 μg/mL for EO and thymol **(18)**, respectively. The treatment of intracellular amastigotes with the EO at concentrations of 25, 50 and 100 μg/mL caused a significant decrease in the survival rate of the parasites, with an IC_{50} value of 34.4 μg/mL. The authors also pointed out that, while thymol **(18)** had low selectivity against promastigotes and showed toxicity to mammalian macrophages, the EO showed low toxicity to mammalian cells, a fact attributed to the protective effect of other constituents.

Study conducted by Farias-Junior et al. (2012) brought the first analysis of the anti-*Leishmania* properties of *L. sidoides* EO, in which carvacrol **(12)** instead of thymol **(18)**, was the main constituent. It was demonstrated that the carvacrol-rich **(12)** EO had an IC_{50} lower than that of the EO whose main constituent was thymol **(18)** against *L. chagasi* promastigotes. Although it is logical to attribute such activity to carvacrol **(12)**, the EO also had 6% of thymol **(18)**, and thus there is a possibility of a synergistic effect between thymol **(18)** and carvacrol **(12)** to explain the greater anti-*Leishmania* effect observed in this EO.

Essid et al. (2015) suggest that the inhibitory activity of carvacrol **(12)** is enhanced in the presence of its isomer thymol **(18)** and its precursors γ-terpene and *p*-cymene **(19)**, as demonstrated by Lambert et al. (2001). In their studies, the EOs of *F. communis*, *T. polium*, and *P. graveolens* reduced by more than 90% the number of parasites in a dose-dependent manner, in the case of *L. infantum* and *L. major*, presenting anti-*Leishmania* activity greater than amphotericin B. The authors

highlight that the mechanism of action of the EOs may involve changes in the mitochondrial membrane.

The relationship between carvacrol **(12)** and p-cymene **(19)** was also suggested by Bouyahya et al. (2017a). In their study, the EO of *O. compactum* extracted from different plant phases (vegetative, flowering and post flowering) showed effective action against three *Leishmania* species in a dose-dependent manner, being the EO obtained in the flowering phase the most active against the three parasites tested. The author also speculated that the involved mechanisms of action may include induction of apoptosis, disruption of the electron transport chain, and inhibition of DNA topoisomerase (Castro et al. 1992).

Monzote et al. (2011) brought another perspective to the action of carvacrol **(12)**. Treatment of *L. amazonensis*-infected murine macrophages with the EO of *Chenopodium ambrosioides* L. proved to inhibit parasite growth. The authors attribute this activity to ascaridol **(20)** and also mention that the toxicity exhibited by the sample could have been caused by the different compounds present in the EO or by the interaction between them. This hypothesis was formulated from the study of Monzote et al. (2009) that showed that ascaridol **(20)** forms a highly reactive carbon-centered free radical. The authors suggested that, through its phenolic hydroxyl group, carvacrol **(12)** serves to attenuate the cytotoxic activity of ascaridol **(20)** by eliminating the free radical (Dapkevicius et al. 2002; Guimarães et al. 2010).

The EOs of *Lippia gracilis* Schauer genotypes 106 and 110 were analyzed and tested against *L. chagasi* promastigotes, resulting in IC_{50} values of 86.32 μg/mL^{-1} and 77.26 μg/mL^{-1}, respectively (de Melo et al. 2013). The authors also showed that thymol **(18)** and carvacrol **(12)**, the main compounds of the EOs, which also had exhibitory activity, and the latter (IC_{50} of 2.3 μg/mL^{-1}) had similar performance to amphotericin B (0.51 μg/mL^{-1}).

Both compounds were also found in the EO of *Z. multiflora*, which showed a significant anti-*Leishmania* effect on the promastigote forms of *L. tropica*. Furthermore, it was shown that the promastigote forms of *L. tropica* without treatment were able to infect 84.1% of macrophages, while promastigotes treated with *Z. multiflora* EO had potency to infect only 11.3% (Dezaki et al. 2016).

Thymoquinone **(21)**, the major compound (43.4%) of the EO of *Nigella sativa* L. (Ranunculaceae), showed an inhibitory capacity for parasitic growth of *L. tropica* promastigotes, with IC_{50}/72 h of 1.16 mg/mL, and *L. infantum*, with IC_{50}/72 h of 1.47 mg/mL, while the EO presented IC_{50}/72 h values of 9.3 mg/mL for *L. tropica* and 11.7 mg/mL for *L. infantum* (Mahmoudvand et al. 2015a). An assay was also carried out to evaluate the inhibition of the infection in macrophages: the promastigotes of *L. tropica* were able to infect only 13 and 27.3%, and those of *L. infantum* infected only 16.3 and 33.6% of the murine macrophages when treated with thymoquinone **(21)** and the EO of *N. sativa*, respectively. However, despite the results showing the high anti-*Leishmania* potential of thymoquinone **(21)**, this coumpound was more cytotoxic compared to EO (Mahmoudvand et al. 2015a).

Forty-four compounds were detected through GC–MS in the EO of *Pluchea carolinensis*; selin-11-en-4α-ol **(22)** (51%) was the major compound (García et al. 2017). In this study, *in vitro* assays for antiparasitic evaluation of the EO showed the

ability to inhibit 100% of the growth of promastigote and amastigote forms of *L. amazonensis* at concentrations of 100 and 200 μg/mL, with a lower IC_{50} on amastigote (6.2 ± 0.1 μg/ mL) than promastigote (24.7 ± 7.1 μg/mL) forms. In *in vivo* models of cutaneous leishmaniasis in BALB/c mice, no mortality or weight loss was observed in the treated groups. The administration of the EO of *P. carolinensis* demonstrated to control the size of the lesions and parasite load of animals infected with *L. amazonensis*. The authors of the work suggest that the results found *in vitro* and *in vivo* on the anti-*Leishmania* effect of EO may be due to the major compound selin-11-en-4α-ol **(22)**, but indicate the need to reiterate analyses with the isolated compound to elucidate its mechanism of action.

Because the intracellular forms of *Leishmania* species complete part of their cell cycle inside macrophages, it is important to establish the selectivity index (SI) of the EO and its components (Moreira et al. 2019). More toxic compounds must be more selective for protozoa than host cells. SI values greater than 1 are considered more selective for activity against parasites, and values lower than 1 are considered more selective for activity against cells.

In their studies, Moreira et al. (2019) established the SI ratio for the EO of *Casearia sylvestris* SW. and its major compound (22.2%) *E*-caryophyllene **(23)**, with values of 2.9 and 5.8, respectively. This was an interesting result, as both were moderately toxic against BALB/c mouse macrophages. The EO presented an IC_{50} of 29.8 μg/mL on *L. amazonensis* promastigotes, better than the result for *E*-caryophyllene **(23)** (49.9 μg/mL). On amastigote forms, *E*-caryophyllene **(23)** had a better result (10.7 μg/mL) than the EO (14 μg/mL) (Fig. 13.2).

13.4.3 Mechanisms of Action

13.4.3.1 Morphological Changes

Chemical analyses revealed 97.9% of α-bisabolol **(24)** in the constitution of the EO of *Vanillosmopsis arborea* (Colares et al. 2013). The compound and the EO showed efficiency in inhibiting the growth of *L. amazonensis* promastigotes with IC_{50}/24 h of 4.95 μg/mL and 7.35 μg/mL, respectively. The parasites showed alterations such as severe cell damage with loss of morphology, discontinuity of the nuclear membrane, increased mitochondrial volume and kinetoplast, and presence of vesicles with an electrondense display with lipid inclusion in the plasma membrane. In addition, the SI, especially for intracellular amastigotes, showed that the compound (9383) was less toxic than the EO (11,526) (Colares et al. 2013). The apoptotic mechanism can be seen in Fig. 13.3.

The above results corroborate the findings of Hajaji et al. (2018), in which α-bisabolol **(22)** isolated from the EO of *Matricaria recutita* L. showed SI values of 5.5 and 6.7 for *L. amazonensis* and *L. infantum* amastigotes, respectively, and IC_{50} of 16.0 ± 1.2 and 9.5 ± 0.1 μg/mL on *L. amazonensis* and *L. infantum* promastigotes, respectively. The researchers demonstrated the ability of the compound to

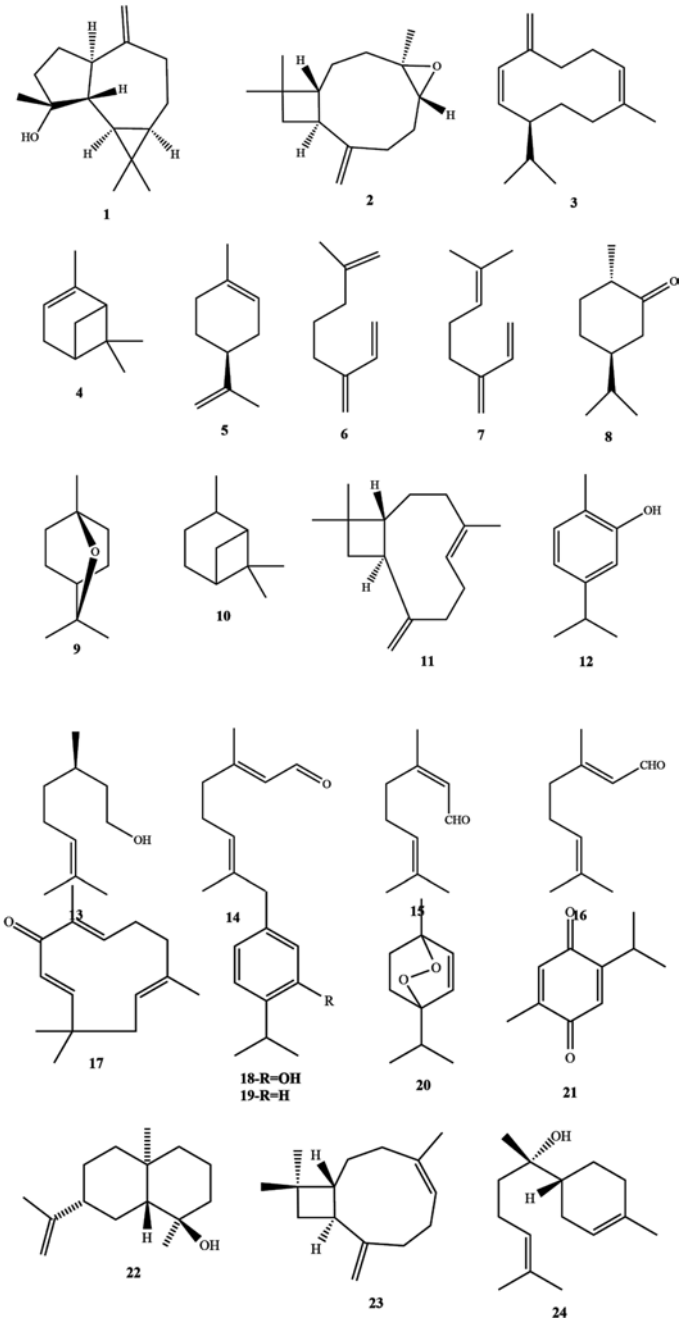

Fig. 13.2 Structural representation of the compounds presented in this section

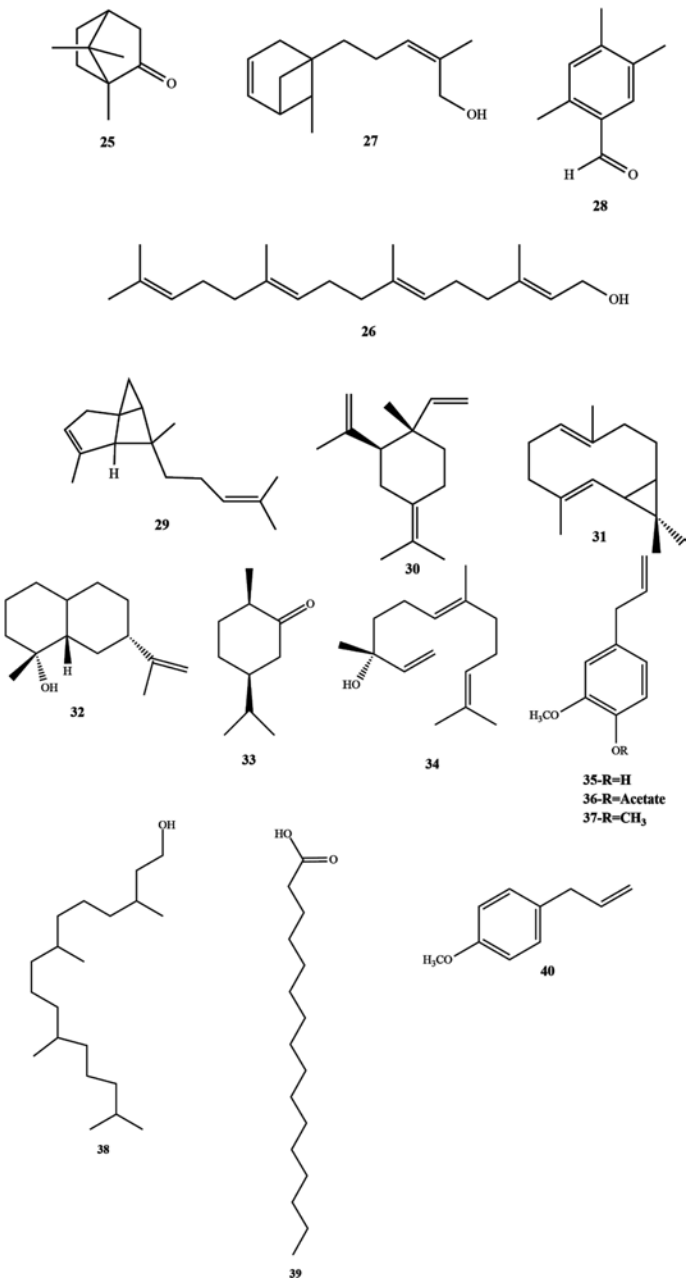

Fig 13.2 (continued)

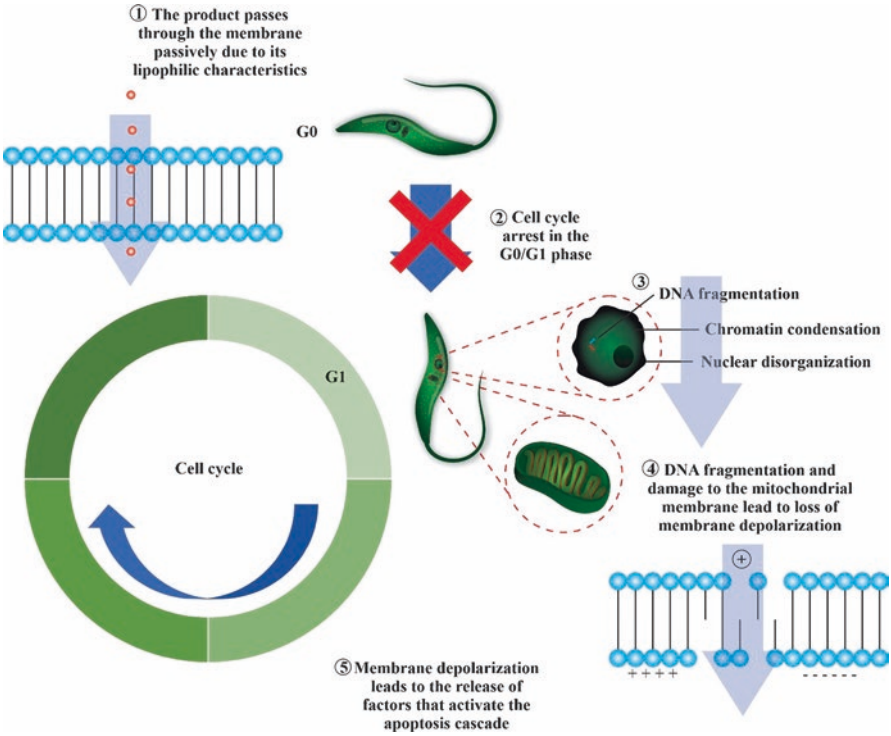

Fig. 13.3 The apoptotic mechanism. (1) The products pass through the parasite membrane passively, due to their lipophilic characteristics; (2) Then, several authors have observed that volatile compounds act by inhibiting the cell cycle in the G0/G1 phase; (3) Phenotypic alterations, such as DNA fragmentation, chromatin condensation and nuclear disorganization, have also been reported, whose images can be found in the studies mentioned in this section; (4) Depolarization of the mitochondrial membrane, which plays a crucial role as a therapeutic target in protists such as *Leishmania*, is the main mechanism promoted by these compounds. (5) Together, these pathways share characteristics responsible for the release of factors that activate the apoptosis cascade, which despite being a programmed process, is the main form of cell death induced by chemical agents

affect plasma membrane permeability without causing necrotic effects, and to activate a programmed cell death process by cellular enhancement of phosphatidylserine externalization and membrane damage, with an apoptosis percentage of 21.66 (IC_{50}) and 40% (IC_{90}) for *L. amazonensis* and 17 (IC_{50}) and 20% (IC_{90}) for *L. infantum* after 24 h of treatment.

The EO of *Cryptocarya aschersoniana* was rich in limonene **(5)** (42%) and had remarkable activity against *L. amazonensis* promastigotes (IC_{50} = 4.46 μg/mL) in the study by Andrade et al. (2018b). However, it was highly toxic to mouse macrophages, with a CC_{50} of 7.71 μg/mL. According to the authors, compounds with CC_{50} below 10 μg/mL are highly toxic, above 10 and below 100 μg/mL are moderately toxic, and above 100 and below 1000 μg/mL are non-toxic. This type of

classification allows evaluating the cytotoxicity of a compound and understanding the mechanisms of action of different substances in their interactions with tissues. The authors recognized that, as this was an *in vitro* test, it did not replicate the actual architecture of the living tissue in which the underlying cells could repair the damage suffered (Andrade et al. 2018b).

The EO from *Vernonia brasiliana* (L.) Druce was rich in terpenes, with the major component being β-caryophyllene **(11)** (Mondêgo-Oliveira et al. 2021). The EO showed activity against *L. infantum* promastigotes, with IC_{50} of 39.01 μg/mL and SI of 1.61, being more toxic to parasites than to DH82 cells. Although the IC_{50} of the standard drug miltefosine was higher (2.54 μg/mL), it was more toxic to DH82 cells, with an SI of 0.55. When tested in combined therapy, there was an antagonistic effect. According to the author, this shows that although both products are bioactive against *Leishmania*, this does not mean that the products will act synergistically. The mechanisms of action of *V. brasiliana* EO were tested and, after 72 hours in contact with *L. infantum* promastigotes at IC_{50} of 39.01 μg/mL, important structural changes were observed, with decreased mitochondrial membrane potential and increased reactive species of oxygen (ROS) production, inducing a late apoptosis.

Although little research has been carried out to identify the mechanisms of action by which EOs and their constituents act, a general analysis of the findings suggests disturbances in the plasma membrane of *Leishmania* causing significant morphological alterations that can induce apoptosis. In the work by Machado et al. (2012a), *C. citratus* EO induced the death of *L. infantum* promastigotes in which depolarization of the mitochondrial potential was observed, involving cell-cycle arrest at the G0/G1 phase and nuclear disorganization, with chromatin condensation. In a study by Aloui et al. (2016), *A. campestres* presented β-pinene **(10)** (32.95%) and was active against *L. infantum* promastigotes (IC_{50} = 44 μg/mL). Furthermore, the EO increased the proportion of cells in the subG0/G1 phase, indicating DNA degradation in promastigotes, suggesting alterations of the apoptotic type.

The EO of *Myrcia ovata* caused growth inhibition of *L. amazonensis*, with a considerable difference at 20 and 30 mg/mL compared to the untreated control (Amorim Gomes et al. 2020). Both concentrations caused 100% inhibition with IC_{50}/96 h of 8.69 mg/mL. The authors observed that after incubation for 3 days with 10 mg/mL of EO, the parasites showed accumulation of lipid bodies, nucleolus disorganization, and the appearance of structures suggestive of autophagosome; and after 4 days of treatment with 5 mg/mL, the parasites showed mitochondrial enlargement (Amorim Gomes et al. 2020). This effect was attributed to the main constituents of the EO geranial **(16)** and neral **(15)**. The effect of citral **(14)**, which is a mixture of geranial **(16)** and neral **(15)** isomers, already tested on *L. amazonensis*, caused ultrastructural changes that included mitochondrial damage and presence of two or more flagella in the parasites, among other effects (Santin et al. 2009).

Neral **(15)** (cis-citral) and geranial **(16)** (trans-citral) together represented about 81% of the EO of *C. citratus*, which was able to kill 65% of *L. infantum* and *L. major* promastigotes and 80% of *L. tropica* promastigotes at a concentration of 50 μg/ml (Machado et al. 2012a). In turn, at the same concentration, citral **(14)** killed about 45% of *L. infantum* and *L. tropica* promastigotes, and about 60% of *L. major*

promastigotes. Furthermore, none of them showed cytotoxicity in bovine aortic endothelial cells and macrophage lineage in the MTT test (Machado et al. 2012a).

The investigations of Sen et al. (2010) showed that promastigotes treated with EO and citral **(14)** showed prominent ultrastructural effects such as the appearance of aberrant-shaped cells with cell body septation, cytoplasmic disorganization, increased cytoplasmic clearance and loss of intracellular content, presence of autophagosomal structures, characterized by intense cytoplasmic vacuolization, in addition to irregular surface with blebs formation and rupture of the membrane. Another factor highlighted is the presence of membrane vesicles in the flagellar pocket, characteristic of an exocytosis process, and it is possible that they resulted from the secretion of abnormal lipids, which accumulate as a consequence of the effect of citral **(14)**. *Cymbopogon citratus* EO and citral **(14)** further promoted sustained mitochondrial membrane depolarization, which is a typical feature of metazoan apoptosis and has been observed to play a key role in drug-induced death in protists such as *Leishmania*. The authors also noted the presence of myelin-like figures as multilamellar bodies, where the nuclear chromatin was organized similarly to the nucleus of apoptotic cells, with disruption of the nuclear membrane. The authors' main hypothesis is that EO and citral **(14)** may have a passive entry and accumulate in the cell membranes of the parasite, leading to an increase in membrane permeability and formation of structures known as autophagosomes (Rodrigues et al. 2002) that are probably involved in an intense process of remodeling of intracellular organelles irreversibly damaged by the EO and citral **(14)**.

Islamuddin et al. (2014a) showed that camphor **(25)** (52.06%) was the major component in the chemical composition of the EO of *Artemisia annua* leaves. The EO exhibited IC_{50} of 14.63 ± 1.49 μg/mL and 7.3 ± 1.85 μg/mL against *L. donovani* promastigotes and amastigotes, respectively. In their evaluations, the authors reported changes in cell morphology, shrinkage in promastigotes that became round in shape, with ruptured flagella and no motility. The apoptosis mechanism was also recognized by the externalization of phosphatidylserine in the cell membrane, evidenced by increased annexin V binding. The authors also observed DNA fragmentation in apoptotic cells, showing an increased proportion of cells in the subG0/G1 phase when treated with *A. annua* EO. Also at the intracellular level, treatment with EO was able to cause depolarization of the parasite's mitochondrial membrane, leading to permeabilization of the inner mitochondrial membrane and consequent release of apoptotic factors.

Monzote et al. (2014b) demonstrated that the EO of *Bixa orellana* presented activity against the intracellular amastigote form of *L. amazonensis*, with IC_{50} of 8.1 μg/mL and SI of 7, and cytotoxic concentration sevenfold higher for the host cells than for the parasites. The EO also showed the ability to control the progression of established cutaneous leishmaniasis in BALB/c mice, with significant differences in lesion size and parasite load between animals treated with EO compared to controls, with no deaths observed after 14 days of application intraperitoneal of the EO. According to the authors, the geranylgeraniol **(26)** present in the composition of the EO (9.1%) may be associated with such activity, since it has been reported that this compound promotes alterations in the mitochondrial structure, including

swelling and formation of circular cristae (Vannier-Santos and Castro 2009). In addition, the compound has also been observed to cause kinetoplast DNA disorganization (Vannier-Santos and Castro 2009) as well as increased superoxide anion production, leading to apoptosis (Lopes et al. 2012).

In the study of the antiparasitic action of the EO of *Lavandula luisieri*, Machado et al. (2019) observed an effect on cell viability in promastigotes of *L. infantum*, with IC_{50}/24 h equal to 63 μg/mL, *L. tropica*, with IC_{50}/24 h equal to 38 μg/mL, and *L. major*, with IC_{50}/48 h equal to 31 μg/mL. In the MTT test, no toxicity was observed at the doses tested (CC_{50} > 200 μg/mL; SI > 3.17). The authors suggest that the action of the EO is linked to oxygenated monoterpenes (75.7%) in its chemical composition, and necrodane derivatives as major compounds (36%). The effects of the EO were verified from image analysis in Scanning Electron Microscope (SEM) and Transmission Electron Microscopy (TEM), in which round and aberrant shapes, cell body septation, disorganization of cytoplasmic organelles, and many autophagosomal structures featured by intense cytoplasmic vacuolization were observed in *L. infantum* promastigotes. The EO was able to induce mitochondria swelling and mitochondrial membrane disorganization indicated by the presence of complex invaginations and formation of concentric membranous structures. These data can be explained by the ability to induce depolarization of the mitochondrial potential, which can promote apoptosis (Arnoult et al. 2002). The arrest of cells in the G0/G1 phase was also detected, with a reduction in the number of cells in the S and G2/M phases; the authors suggested that this may have occurred due to an decrease in mitochondrial membrane potential and since this reduces the energy available.

The analysis of the EO of *Eremanthus erythropappus* conducted by Amorim Gomes et al. (2020) revealed the presence of 13 constituents, corresponding to 94.22% of its composition, with 85.98% of α-bisabolol **(22)**. The authors verified a percentage of inhibition of *L. amazonensis* promastigotes of 35% under concentrations of 5 and 10 mg/mL of *E. erythropappus* EO, and almost 100% inhibition using concentrations higher than 20 and 30 mg/mL after 96 h of treatment, with IC_{50}/96 h of 9.53 mg/ml. The ultrastructural analysis showed that after 3 days of incubation with 10 mg/mL of EO, the parasites showed accumulation of lipid bodies, demonstrating a possible mechanism of action of the compound.

De Medeiros et al. (2011) also pointed out that the treatment with *L. sidoides* EO induced remarkable changes in the morphology of the parasites, particularly the accumulation of large lipid droplets in the vicinity of the plasma membrane. At high EO concentrations, membrane disruption, increased lipid electron density, and loss of cytoplasmic content, alterations compatible with loss of cell viability and cell death by necrosis (Menna-Barreto et al. 2009), were also observed. Furthermore, characteristics such as parasite swelling, presence of wrinkled or ruptured membranes, and loss of cytoplasmic material in promastigotes were present, supporting the deleterious effects of EO on the plasma membrane so widely disseminated in the literature. The hypothesis of the authors is that the constituents of the EO penetrate into the cell and impair the ergosterol biosynthesis pathway, and they may also react directly with the membrane through their reactive hydroxyl portion. Thus, the

extensive membrane damage may be due to a combined effect of the two events (Nafiah et al. 2011).

Subsequently, Monzote et al. (2014a) demonstrated that NADH- and succinate-dependent reduction of cytochrome-C was inhibited in mitochondrial fractions of *L. amazonensis* and liver mitochondria from BALB/c mice in the presence of *C. ambrosioides* EO and its pure major compounds, carvacrol **(12)** and thymol **(18)**.

Their findings suggested that such reduction was not specifically sensitive to EO in *Leishmania* mitochondria, however, the existence of other more sensitive and more selective targets, such as mitochondrial membrane potential, was not ruled out. The authors could not establish whether the loss of mitochondrial membrane potential was a primary effect of EO (directly influencing mitochondrial functions) or arose subsequent to other cellular effects triggering apoptosis via mitochondria. Furthermore, they suggested that other parasite damages caused by EO such as free radical-triggered DNA or protein-alterations, or parasite-specific transporters such as the P2 amino-purine transporter (De Koning 2001), DNA triggered by free radicals or protein alterations, or parasite-specific transporters, such as the P2 amino-purine transporter (De Koning 2001), could contribute to specific killing of *Leishmania*.

Tasdemir et al. (2019) performed tests with both carvacrol **(12)** and thymol **(18)**, the main constituents of the EO of *Origanum onites*, reporting for the first time their effect on *L. donovani* amastigotes. The authors suggested that the EO permeates the cell membrane and kills parasites by affecting the cytoplasmic metabolic pathways or organelles, and not by compromising the integrity of the parasite's membrane, as presented by several studies in this section. They reached this conclusion based on a flow cytometry study performed by Santoro et al. (2007) and also highlighted the importance of the presence of the hydroxyl group in the bioactivity of phenolic compounds such as carvacrol **(12)** and thymol **(18)** (Dorman and Deans 2000; Ultee et al. 2002).

13.4.3.2 Immunological Changes

The evaluation of the EO of *Pseudotrachydium kotschyi* revealed the presence of Z-α-trans-bergamotol **(27)** (23.25%), durylaldehyde **(28)** (16.07%), and α-bergamotene **(29)** (10.48%) (Ashrafi et al. 2020a). It was observed that the EO had anti-*Leishmania* potential at a concentration of 5000 μg/mL and suggested that these compounds are involved in the biological activities of the oil, for it was observed that EO was able to protect macrophages against infection by promastigotes. Their data indicated that EO exerts anti-*Leishmania* activity by affecting the levels of TNF-α and TGF-β1 in macrophages. These cytokines were determined in *Leishmania*-infected macrophages after treatment with EO. The immunological mechanism can be seen in the Fig. 13.4.

The EO of *Artemisia absinthium* inhibited the *in vitro* growth of *L. amazonensis* promastigotes and amastigotes, with IC_{50} of 14.4 ± 3.6 μg/mL and 13.4 ± 2.4 μg/mL, respectively (Monzote et al. 2014c). The activity *in vivo* was evaluated in a

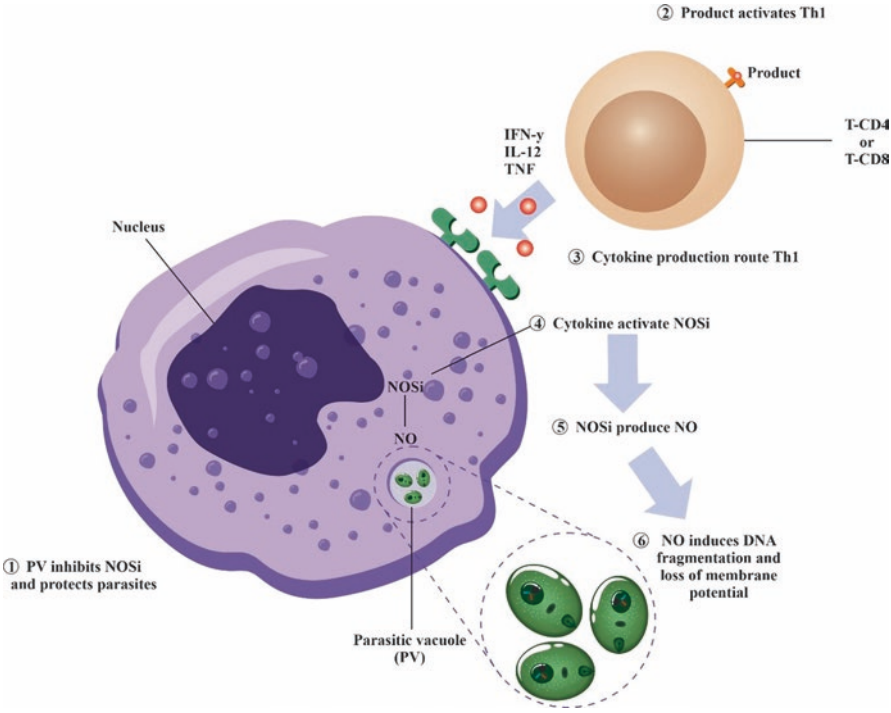

Fig. 13.4 Modulation of the immune response by essential oils and their compounds. (1) Parasitophorous vacuoles (PV) contain a plasma membrane and may represent a specific adaptation to minimize the toxic effects of reactive nitrogen intermediates generated by the host cell. (2) The modulation of the response occurs in cells with a T-helper type 1 (Th1) cytokine profile. (3) This profile is associated with the production of cytokines such as IFN-γ, IL-12 and TNF. (4) These cytokines lead to the activation of anti-*Leishmania* activities, mainly through the activation of the inducible nitric oxide synthase (iNOS) enzyme. (5) The production of nitric oxide (NO) induces an oxidative explosion in infected cells. (6) This oxidative explosion is associated with the process of loss of the parasite's mitochondrial membrane potential, however, it can also cause extensive nuclear DNA fragmentation in axenic and intracellular amastigotes

model of cutaneous leishmaniasis in BALB/c mice, where control of lesion size and parasite burden was observed. Furthermore, no evidence of mortality in the treated groups or weight loss greater than 10% were observed during the study. The authors suggested that *Artemisia* EO may improve Th1 immune responses and microbicide activation of macrophages.

Nunes et al. (2021) found 69.76% of hydrocarbon sesquiterpenes in the EO of *Eugenia piauhiensis* Vellaff. (Myrtaceae), with 23.5% being γ-elemene **(30)** and 11.94% (*E*)-β-caryophyllene **(23)**. The EO and the isolated compound γ-elemene **(30)** presented greater activity against amastigote (EC_{50} = 4.59 ± 0.07 μg/mL and 8.06 ± 0.12 μg/mL, respectively) than promastigote (IC_{50} = 6.43 ± 0.18 μg/mL and 9.82 ± 0.15 μg/mL, respectively) forms of *L. amazonensis*. The authors suggested that this difference could be indicative of immunomodulatory activity and

macrophage activation, as experiments of macrophage infection models *in vitro* revealed increased levels of TNF-α, IL-12, NO, and ROS in the supernatant of *L. amazonensis*-infected macrophages, suggesting an activation of the Th1 (not Th2) profile, a mechanism that has been the objective of anti-*Leishmania* drugs.

In the work by Carvalho et al. (2017), the EO of *Myracrodruon urundeuva*, rich in myrcene **(6,7)** (α-myrcene **(6)** 37.23% and β-myrcene **(7)** 42.46%), caused morphological changes such as cells with rounded or completely spherical shapes, with the presence of cell debris, typical of cell lysis. Furthermore, the results obtained against both forms of *L. amazonensis* (IC_{50} = 205 μg/mL for promastigotes; 104.5 μg/mL for axenic amastigotes; 44.5 μg/mL for intracellular amastigotes) suggest an increase in the phagocytic capacity of macrophages. According to the authors, this increase can be triggered by immunomodulatory mechanisms. One way to assess this activity is by determining the NO content. NO production is stimulated by protective cytokines, such as IFN-γ, and is extremely reactive, causing damage to the parasite's proteins and DNA. However, their tests with the EO of *M. urundeuva* did not promote NO production, suggesting that phagocytosis was not stimulated by immunomodulatory mechanisms.

In line with the immunomodulator role of NO, Jihene et al. (2020) showed that *Leishmania*-infected macrophages produced 36.8% more NO than uninfected ones. Furthermore, uninfected macrophages treated with 14.76, 7.38 and 3.69 μg/mL of propolis EO produced 50.4%, 38.1% and 25% respectively more NO than control cells. Macrophages infected and treated with EO showed a significant increase in NO levels, reaching 230% at the highest concentration.

The EO of *Nectranda hihua*, composed mainly of sesquiterpenes (89%), especially bicyclogermacrene **(31)** (28.1%), showed activity against intracellular *L. infantum* amastigotes (IC_{50} = 0.2 ± 1.1 mg/mL). The SI values were 249.4 and 149.0 for murine fibroblasts and macrophages, respectively, reflecting the oil's highly selective action on amastigote forms. The EO of *Nectranda gardneri* was active in intracellular amastigotes of *L. infantum* and *L. amazonensis* (IC_{50} = 2.7 ± 1.3 and 2.1 ± 1.06 mg/mL, respectively), with low cytotoxicity. This EO was also composed mainly of sesquiterpenes (85.4%), with intermediol **(32)** being the main component (58.2%) (Bosquiroli et al. 2017). The authors observed that the EO of the two species induced a significant increase in NO production by *L. amazonensis*-infected cells, however, in the case of *L. infantum*, only the EO from *N. gardneri* was active, suggesting that the anti-*Leishmania* activity of the EO may be associated with this important mechanism (Olekhnovitch and Bousso 2015).

Bosquiroli et al. (2015) demonstrated the inhibition of proliferation of intracellular amastigotes 24 h after the EO of *Piper angustifolium* was added to infected cells. The infection rate decreased in a range of 88.1 to 100% from the lowest to the highest concentration, with an IC_{50} of 1.43 μg/mL for *L. infantum* and low cytotoxicity for mammalian cells compared to amphotericin B, although the latter is more active. A significant increase in NO release was found after treatment with the EO at concentrations of 6.25 and 12.5 μg/mL; however, at concentrations of 25 and 50 μg/mL, the EO did not induce a significant increase in NO release, showing an atypical result that may be due to the presence of certain compounds in the EO.

The EO of *Curcuma longa* expressed anti-*Leishmania* action against promastigote and amastigote forms of *L. amazonensis* (Teles et al. 2019). The concentration of 125 μg/mL generated a decrease of 80.73% of promastigote and 40.75% of amastigote forms in infected cells. In terms of possible mechanisms of action, the authors evaluated the production of nitrite, an indirect measure to quantify NO. They found that the EO inhibited the production of NO in macrophages. Thus, the authors suggested the existence of other possible mechanisms involved in the activity of *C. longa* EO against intracellular amastigotes yet to be investigated.

13.4.3.3 Antioxidants

Since the loss of membrane balance can lead to the entry of ions into the cells, causing polarization changes; verifying the antioxidant capacities of EOs may serve to detetct this activity. According to Bouyahya et al. (2017b), antioxidant tests serve to express mechanisms of action involving polarization and chemical behavior in the presence of the product being tested.

Ahmed et al. (2011) found the compound camphor **(25)** (13.82%) in the composition of the EO of *Thymus hirtus sp. Algeriensis* and verified its anti-*Leishmania* activity. They found an IC_{50} of 0.43 μg/mL for *L. major* promastigotes and 0.25 μg/mL for *L. infantum* promastigotes. The composition and anti-*Leishmania* activity of the EO of *Ruta chalepensis* was investigated in the same study, highlighting the presence of 84.28% of 2-undecanone, and inhibitory action only against *L. infantum* promastigotes. Their tests to assess antioxidant potential through DPPH free radical scavenging showed a low antioxidant power for the EO, suggesting that anti-*Leishmania* activity was not correlated with antioxidant activity of the EO.

High concentrations of camphor **(25)** (36.82%) and compounds such as *α*-thujone **(33)** (7.65%) and *β*-thujone **(8)** (7.21%) were found in the EO of *A. herba-alba* (Aloui et al. 2016). The EO was tested against promastigote forms of *L. infantum*, revealing inhibitory power with an IC_{50} of 68 *μ*g/mL. Antioxidant capacity by DPPH radical scavenging, with an IC_{50} of 9.1 mg/mL, and intense reducing capacity by the of ferric reducing antioxidant power (FRAP) assay, with a result of 27.48 mM Fe2+, were also observed. The effect of the EO on the cell membrane assessed through measurement of lactate dehydrogenase showed no induction of cytolysis even after prolonged incubation time (72 h). Flow cytometric analysis of *L. infantum* promastigotes detected DNA degradation by the increase in the proportion of cells in the sub-G0/G1 phase between the applied doses, followed by a decrease in the number of cells in the S and G_2/M phases. Annexin V/7-ADD staining showed that treatment with the EO caused the parasites to express apoptotic profiles without inducing necrosis.

13.4.3.4 Enzymatic Activity

According to the study by Marques et al. (2011), the EO of *Piper claussenianum* leaves was rich in sesquiterpenes, with nerolidol **(34)** being the major component (81%), and caused 62.17% inhibition in the levels of arginase activity. Pretreatment of *L. amazonensis* promastigotes with the EO reduced the percentage of macrophage infection by 42.7%, and the treatment of already infected macrophages promoted a reduction of 31.25% of the infected cells. Cytotoxicity of the EO in macrophage and fibroblast cell lines was absent at concentrations ranging from 40 to 0.56 mg/mL. The authors also performed treatment with the EO of *P. claussenianum* and INF-γ together, which provided an increase in NO production of 20.5% in cells infected with *Leishmania*. Such production was considered by the authors as a useful strategy for infection control by inhibiting arginase activity levels in the parasite.

In parasites of the genus *Leishmania*, arginase activity is essential for the growth of the protozoans (Vincendeau et al. 2003; Roberts et al. 2004) in addition to being associated with cytotoxic processes and immunological mechanisms due to the role in NO synthesis (Kanyo et al. al. 1996; Da Silva et al. 2002). Thus, arginase activity is a potential target of anti-*Leishmania* pharmacological compounds.

Oxygenated monoterpenes, especially 1,8-cineole **(9)** (23.6%) and camphor **(25)** (18.7%), were predominant in the EO of *Rosmarinus officinalis* L. (Bouyahya et al. 2017c). In chemical analyses of the EO of *Melaleuca leucadendra* L. (Myrtaceae), there was 61% of 1,8-cineole **(9)** (Monzote et al. 2020b). In their assays with *L. amazonensis*, the authors demonstrated that 1,8-cineole **(9)** had an IC_{50} value of 68.3 ± 3.4 μg/mL and no cytotoxicity against macrophages at 200 μg/mL. Despite this, the authors did not associate the antiprotozoal activity to the compound, suggesting that the activity of the EO may result from complex interactions between its constituents, and that even components in smaller amounts can play a critical role.

In a computational analysis of the structure and binding of 1,8-cineole **(9)** isolated from *Croton nepetifolius* EO in relation to the enzyme *L. infantum* trypanothione reductase (LiTR), in the structural representation of LiTR coupled to 1,8-cineole **(9)**, favorable interactions of different types were formed, as Van der Waals, hydrophobic and hydrogen bonds, with participation of 7 residues (Gly197; Tyr221; Arg222), and the ligand established H bonding interaction with Gly196 within a radius of 3.68 Å (Morais et al. 2019). Turkano et al. (2018) demonstrated the RT inhibition of the compound 2-(diethylamino)ethyl 4-((3-(4-nitrophenyl)-3-oxopropyl)amino)benzoate with the participation of the residues Tyr221, Gly197, Asn254, Arg222, and Arg228, which are essential for LiTR inactivation, suggesting a possible mechanism of action against the *Leishmania* species tested.

13.4.4 Other Compounds Present in Essential Oils

Although most results point to terpenes as the main constituents present in EOs, other compounds, such as phenylpropanoids, have shown strong anti-*Leishmania* activity. One of the main representatives of this class is eugenol **(35)**.

In a research carried out by Moemenbellah-Fard et al. (2020), 33 components were identified in the EO of *Syzygium aromaticum*, and among the main ones, eugenol **(35)** (65.41%), trans-caryophyllene (12.06%), eugenol acetate (9.85%), and caryophyllene oxide **(2)** (3.0%) stood out. The EO and eugenol **(35)** were tested as for their antiparasitic activity against *L. major* promastigotes, reaching IC_{50} values of 654 μg/mL and 517 μg/mL, respectively, and against *L. tropica* promastigotes, with IC_{50} of 180 μg/mL and 233 μg/mL, respectively.

In the studies by Islamuddin et al. (2013), the EO of *S. aromaticum* revealed a concentration of 59.75% of eugenol **(35)** and 29.24% of eugenyl acetate **(36)**. The authors found an anti-*Leishmania* effect against intracellular promastigote and amastigote forms of *L. donovani*, with IC_{50} of 21 mg/mL and 15.24 mg/mL, respectively. In this study, it was indicated that EO-induced cell death occurred due to loss of membrane integrity, with evidence indicating late apoptosis. The authors also reported that EO-treated promastigotes exhibited a hypodiploid peak in subG0/G1, and the parasites presented reduced DNA content, thus confirming the occurrence of DNA fragmentation and induction of apoptosis. It is noteworthy that the mechanisms of action presented were similar to those presented by terpene-rich EOs.

Analysis of the EO of *Ocimum gratissimum* identified the presence of 86.5% of eugenol **(35)** (Le et al. 2017). This EO had its anti-*Leishmania* activity against *L. mexicana* tested using concentrations of 25 and 50 nL/mL, with IC_{50} of 4.85 nL/mL. Cytotoxicity tests showed survival of more than 80% of the analyzed mammalian cells after 72 hours, at the maximum concentration used (Le et al. 2017).

Methyl-eugenol **(37)** was reported as the major compound (33.89%) of the EO of *C. nepetifolius,* followed by *E*-caryophyllene **(23)** (21.23%) and 1,8-cineole **(9)** (10.44%). According to Morais et al. (2019), these compounds were likely responsible for the anti-*Leishmania* activity of the EO at concentrations of 100, 50, 25, 12.5, and 6.25 μg/mL against *L. amazonensis* ($IC_{50} = 9.87 \pm 2.21$ μg/mL) and *L. braziliensis* ($IC_{50} = 9.08 \pm 2.59$ μg/ml). In addition, at the concentration of 100 μg/mL, the EO presented toxicity against macrophages statistically similar to amphotericin B. It is important to note that, although the largest fractions of these EOs are phenylpropanoids, there are terpenes in considerable concentrations present in their composition.

This is the case of the EO of leaves of *Scheelea phalerata* Mart. ex Spreng (Arecaceae). The EO had phytol **(38)** as a major compound in percentages of 36.7% and 26.1% in plants collected in the dry and rainy seasons, respectively; the EO extracted in the rainy season also presented 18.7% of palmitic acid **(39)**, as found in the work of Oliveira et al. (2020). Nevertheless, only the EO extracted in the rainy season had an effect against *L. amazonensis* promastigotes ($IC_{50} = 165.05 \pm 33.26$ μg/mL). The authors suggested the role of compounds produced in this season in the

inhibitory effect on parasites, emphasizing a synergistic action between the main components of the EO, phytol **(38)** and palmitic acid **(39)**, since the EO extracted during the dry season showed a higher concentration of phytol **(38)** but no anti-*Leishmania* activity. Another hypothesis addressed in the study was based on the possibility that other compounds present in the EO are capable of altering the activity of phytol **(38)** by the formation of compounds, promoting the inactivation of the molecule.

The compound methyl chavicol, also called estragole **(40)**, was found in the EO of *Tagetes lucida* Cav., constituting approximately 97% of the oil. The EO was tested against *L. tarentolae* promastigotes, resulting in an IC_{50} of 61.4 ± 2.4 μg/mL, and against *L. amazonensis* promastigotes, with an IC_{50} of 118.8 ± 1.2 μg/mL. Estragole **(40)** proved to be more effective than the EO, with an IC_{50} of 28.5 ± 1.0 μg/mL and 25.5 ± 3.3 μg/mL for *L. tarentolae* and *L. amazonensis*, respectively (Monzote et al. 2020a). The authors observed that the EO promoted inhibition of oxygen consumption in *L. tarentolae* at the maximum tested concentration of 100 μg/mL; however parasites treated with estragole **(40)** remained with normal oxygen consumption, suggesting that the EO targets the mitochondria of protozoa. Furthermore, estragole **(40)** was able to cause mitochondrial rupture. The authors suggested that the molecule acts as a mitochondrial uncoupler, although it is only a weak inhibitor of mitochondrial electron transfer in *Leishmania*.

13.4.5 Other Applications

Other forms of application for EOs have been explored, as in the case of EO eluted in nanoemulsions and nanogel. These mixtures can be used topically, improving the pharmacodynamic profiles of the product. In the study by Ghanbariasad et al. (2021a), the EO from *Citrus sinensis*, whose major compound was limonene **(5)** (71.26%), was used against *L. tropica* and *L. major* promastigotes, and IC_{50} values of 151.13 μg/mL and 108.31 μg/mL, respectively, were observed. Then, the nanogel based on *C. sinensis* nanoemulsion was prepared to improve its stability. According to the author, the advantage of converting nanoemulsions into nanogels is the increase in viscosity, which promotes the accumulation of the solution and improves the hydration of the application site. The nanometric dispersion of the EO and the better hydration lead to better penetration of the EO in to the locality. It is suggested that this type of application could also prevent the entry of environmental pathogens into the lesion, reducing the chance of secondary infection. In tests, the viability against *L. major* and *L. tropica* was reduced to less than 10% when used at a concentration of 9.15 mg, which was a better result than that obtained with EO alone in topical application (Ghanbariasad et al. 2021a).

13.4.6 Perceptions, Conclusions and Perspectives

Although EOs are presented as important candidates in the search for new anti-*Leishmania* drugs, we observed that some steps are still needed, especially considering that most studies did not perform the *in vivo* analyses necessary to identify the main characteristics of the compounds (bioavailability, pharmacokinetics, pharmacodynamics etc.) in new pharmacological approaches. The investigation of compounds in *in vivo* assays is essential to leverage new therapeutic hypotheses, since many compounds are discarded for not showing results *in vivo* or *in vitro*, as discussed by Brito et al. (2013). However, the authors emphasize that the mechanisms of action and interaction of drugs in humans are often discovered after their indication and use.

Another important highlight is that the evaluations presented in this section used the promastigote form to screen the most prominent compounds, probably due to handling, cost and duration of the tests. However, it is important to mention that studies conducted with amastigotes cultivated in macrophages are considered the best choice for evaluating the potential of the compounds in initial evaluation models, although, in experimental stages of sandflies, for example, there is no difference between promastigotes and amastigotes as to the development of the infection, as observed by Fampa et al. (2021) in *L. donovani*. This condition is important, considering that the morbidity and mortality associated with *Leishmania* is caused by this evolutionary form (Brito et al. 2013).

This question is evident in the studies by Tasdemir et al. (2019) who found discrepancies between the efficacy of thymol **(18)** and carvacrol **(12)** *in vitro* and *in vivo*, with reduced effects in animals. The authors attributed this result to non-ideal pharmacokinetics and physicochemistry, such as very fast absorption, low solubility, low bioavailability and elimination rate, considered the main obstacles in the development of drugs from the EO and its volatile components (Wang et al. 2009; Nagoor Meeran et al. 2017).

Despite the importance of the initial investigation of compounds, it is important to mention that some authors leave clues about the steps to follow after their studies, through the elucidation of some mechanisms of action. They cited, for example, the release of NO or the observation of the ultrastructural effects of compounds on the parasites. Although there are cost and equipment limitations, it is important to set a path for future investigations of active substances, minimizing secondary studies aimed at screening mechanisms, which are important due to the phenotypic and genotypic differences presented by the *Leishmania* species used in the bioassays.

Another alternative is presented by Andrade-Ochoa et al. (2021) who, based on the varied chemical structures and biological activities exhibited by the compounds, suggested the use of *in silico* methodologies to identify different therapeutic targets for EO constituents. Analyses performed by Ogungbe and Setzer (2013) provided evidence of the interaction of different structural types of terpenoids with certain targets in *Leishmania* that may support new phytochemical investigations and synthetic modifications in compounds or the synthesis of new antiparasitic structures.

It is possible to conclude that the anti-*Leishmania* activity of EOs stems from to the lipophilic character of their constituents, such as terpenes and phenylpropanoids, which can passively cross the membranes and disturb the osmotic balance of the cells. This may partly explain why many of the EOs have a certain degree of toxicity for mammalian cells. Given the few studies that have tested the mechanisms of action of EOs, research aimed at elucidating these bioactivities is necessary.

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