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The leishmanicidal activity of essential oils: A systematic review

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ABSTRACT

Leishmaniasis is the neglected disease among parasitic diseases with an increasing rate of infections. Recently, numerous studies have been conducted on the leishmanicidal properties of various essential oils (EOs). In this research, literature have been systematically reviewed, from 20 years ago, and required information have been extracted. Overally, leishmanicidal effects of ~180 EOs against promastigotes of nine species of *Leishmania* have been documented. Inhibitory concentrations 50% (IC50) of around 30 EOs were less than 10 μg.mL^{-1}. EOs of *Tetradenia riparia*, *Nectandra hihua*, and *Thymus hirtus* with IC50s of 0.01, 0.20, and 0.25 μg.mL^{-1} against *Leishmania amazonensis*, *Leishmania infantum*, and *Leishmania major* respectively, were identified as the most effective EOs. Furthermore, IC50 of *Thymus hirtus* on *Leishmania infantum* was 0.43 μg.mL^{-1}. Frequently, substantial differences were found between the observed IC50s of one EO against promastigotes of different species of *Leishmania*. It can be concluded that the leishmanicidal activity of EOs is selective. Turning to the results, the combination of EOs for the design of multifunctional drugs can lead to excellent outcomes. Interestingly, the results have been classified by promastigote species, so this would be a valuable benchmark for researchers.

Implication for health policy/practice/research/medical education:
This review provided a detailed insight into the leishmanicidal activities of around 180 plant-derived essential oil and showed that some of them could be used as a reliable source for developing new drugs or nano/formulations.
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Introduction

Leishmaniasis is one of the most important vector-transmitted diseases which has the second rank after malaria in terms of mortality caused by a parasite disease (1). Leishmaniasis is currently endemic in 102 countries. Countries such as Iran, Afghanistan, Syria, Algeria, North Sudan, Ethiopia, Peru, Colombia, Costa Rica, and Brazil have the highest incidence of leishmaniasis (2,3). An estimated 700 000 to 1 million new cases, and 26 000 to 65 000 deaths occur, annually (4).

Leishmaniasis is caused by an obligate intracellular parasite of the genus *Leishmania* (Trypanosomatida) (5) and transmitted by the bite of infected females of sand flies (Family: Phlebotominae) (6). This disease can be seen in various forms, including cutaneous, visceral, and mucosal leishmaniasis (7). *Leishmania* parasites have two forms in their life cycle, including amastigote and promastigote (8).

Considering the growing number of new cases, the development of new drugs is critical. Plant-derived essential oils (EOs) are natural oil that secreted as secondary metabolites from different parts of the aromatic plants (9). EOs composed of a mixture of hydrophilic and hydrophobic molecules (10). They possess various biological activities such as larvicidal effect (11), antibacterial properties (12), and antifungal aspect (13), and introduces an excellent source for finding new drugs (14).

Recently leishmanicidal activities (LCA) of EOs have received much attention. Moreover, their effects on promastigotes of different species of *Leishmania* have been

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reported frequently (15,16). In this research, the LCA of EOs on different types of promastigotes systematically have been reviewed, form January 1, 2000 to June 30, 2019.

Data collection

Due to much publication on investigating LCA of EOs, data collection was included just to PubMed website (https://www.ncbi.nlm.nih.gov/pubmed/advanced). Steps for finding proper reports were described as follow:
A: Included dates: 2000.01.01 - 2019.06.30.
B: *Leishmania**[Title/Abstract]
C: Essential oil*[Title/Abstract]
D: *Leishmania**[Title/Abstract]) AND essential oil*[Title/Abstract]: 120 docs.

Full texts of all 120 papers were collected. Required information including scientific names of plants, parts of used for EOs extraction, and inhibitory concentration 50% (IC50) were also extracted. Fifty-five articles that had no reported IC50 were excluded. It should be noted that IC50 is a quantitative measure that indicates how much of an EO is needed to inhibit 50% of promastigotes growth in comparison to control groups, no treated with EO.

Leishmanicidal activity of essential oils

LCA of 179 EOs on promastigotes of 9 species of *Leishmania* was extracted from 66 documents. Those species were *L. amazonensis* (71 reports), *L. braziliensis* (15 reports), *L. chagasi* (14 reports), *L. donovani* (8 reports), *L. infantum* (17 reports), *L. major* (31 reports), *L. mexicana* (9 reports), *L. panamensis* (9 reports), and *L. tropica* (5 reports). Collected information about each species was listed in tables of 1-9 as follows:

LCA of EOs on promastigotes of *L. amazonensis* was listed in Table 1. *L. amazonensis* is an etiological agent of human cutaneous leishmaniasis in the Amazon region of Brazil from New World (17). The most potent EO was *Tetradenia riparia* with IC50 of <1 μg.mL^{-1} (18-20). Interestingly, LCA of 15 other EOs including *Cymbopogon citratus, Eugenia uniflora, Nectandra gardneri, Protium ovatum, Chenopodium ambrosioides, Eugenia uniflora, Chenopodium ambrosioides, Chenopodium ambrosioide* (Wild Type), *Cryptocarya aschersoniana, Ocotea dispersa, Chenopodium ambrosioide, Nectandra megapotamica, Chenopodium ambrosioide, Anillosmopsis arborea,* and *Achillea millefolium* were lower than 10 μg.mL^{-1}. These mentioned EOs are excellent candidates for the development of new drugs.

Table 2 contains a list of EOs with their IC50s on promastigotes of *L. braziliensis*; in the new world is causative agents of cutaneous leishmaniasis (51). Among the examined EOs, IC50 (μg.mL^{-1}) of 3 EOs were lower than others; *Lantana camara*: 72.30 (52), *Piper aduncum:* 77.90 (53), and *Piper auritum*: 52.10 (54).

The most common form of leishmaniasis is cutaneous leishmaniasis, which causes several types of skin lesions on exposed parts of the body such as ulcers, leaving life-long scars and severe disability or stigma (55,56).

Table 3 reports the LCA of many EOs against *L. chagasi*.

Table 1. Leishmanicidal activities of EOs on promastigotes of *Leishmania amazonensis*

Plant name	Part(s) of use	IC50 (μg.mL^{-1})	References
Achillea millefolium	Leaves/ flowers	7.80	(21)
Aloysia gratissima	Aerial part	25.00	(22)
Artemisia absinthium	Leaves	21.50	(23)
Artemisia absinthium	Leaves	14.40	(24)
Bulnesia sarmientoi	Leaves/ stems	85.50	(25)
Cananga odorata	Leaves/ stems	NSV*	(25)
Chenopodium ambrosioides	Green leaves	2.90	(26)
Chenopodium ambrosioides	Dry leaves	20.70	(26)
Chenopodium ambrosioide (After IP treatment)	Aerial parts	6.71	(27)
Chenopodium ambrosioide (After O treatment)	Aerial parts	5.55	(27)
Chenopodium ambrosioide (wild type)	Aerial parts	3.74	(27)
Chenopodium ambrosioides	N/A	3.70	(28)
Cinnamodendron dinisii	Leaves/ stems	54.00	(25)
Cinnamomum camphora	Leaves/ stems	NSV	(25)
Cinnamomum zeylanicum	Leaves	NSV	(29)
Cordia verbenaceae	Leaves/ stems	64.70	(25)
Coriandrum sativum	Seeds	19.10	(30)
Cryptocarya aschersoniana	Leaves	4.46	(31)
Curcuma longa	Aerial parts	405.50	(29)
Cymbopogon citratus	Leaves	1.70	(32)
Elettaria cardamomum	Leaves/ stems	NSV	(25)

Table 1. Continued

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Eugenia uniflora	Leaves	3.04	(33)
Eugenia uniflora	Leaves	1.75	(33)
Ferula galbaniflua	Leaves/ stems	95.70	(25)
Foeniculum officinalis	Leaves/ stems	328.20	(25)
Gualtheria fragrantissima	Leaves	22.20	(30)
Lavandula officinalis	Leaves/ stems	NSV	(25)
Lippia sidoides	Aerial parts	44.38	(34)
Litsea cubeba	Leaves/ stems	NSV	(25)
Matricaria chamomilla	Leaves/ stems	60.10	(25)
Melissa officinalis	Leaves/ stems	132.00	(25)
Myracrodruon urundeuva	Leaves	205.00	(35)
Myroxylon peruiferum	Leaves/ stems	162.20	(25)
Nectandra amazonum	Leaves	22.10	(36)
Nectandra gardneri	Leaves	2.10	(36)
Nectandra megapotamica	Leaves	6.66	(37)
Nectandra megapotamica	Leaves	21.30	(36)
Ocimum gratissimum	Leaves	135.00	(38)
Ocotea dispersa	Leaves	4.67	(39)
Ocotea odorifera	Leaves	11.67	(39)
Origanum vulgare	Aerial parts	308.40	(29)
Pelargonium graveolens	Leaves/ stems	363.70	(25)
Piper aduncum	Leaves	19.30	(40)
Piper aduncum.	Leaves	25.90	(41)
Piper arboretum	Leaves	15.20	(41)
Piper cernuum	Leaves	27.10	(41)
Piper claussenianum	Leaves	30.40	(42)
Piper claussenianum	Inflorescence	NSV	(42)
Piper cubeba	Fruits	326.50	(43)
Piper demeraranum	Leaves	86.00	(44)
Piper diospyrifolium	Leaves	13.50	(41)
Piper duckei	Leaves	46.00	(44)
Piper gaudichaudianum	Leaves	93.50	(41)
Piper mikanianum	Leaves	NSV	(41)
Piper mosenii	Leaves	17.40	(41)
Piper ossanum	Leaves	NSV	(40)
Piper rivinoides	Leaves	10.90	(41)
Piper xylosteoides	Leaves	NSV	(41)
Pluchea carolinensis	Leaves	24.70	(45)
Protium ovatum	Leaves	2.280	(46)
Salvia sclarea	Leaves/ stems	325.90	(25)
Siparuna guianensis	Leaves/ stems	48.50	(25)
Syzygium cumini	Leaves	36.00	(47)
Syzygium cumini	Leaves	60.00	(47)
Syzygium cumini	Leaves	115.00	(47)
Syzygium cumini	Steam	19.70	(48)
Tetradenia riparia	Leaves	0.53	(20)
Tetradenia riparia	Leaves	0.03	(19)
Tetradenia riparia	Leaves	0.01	(18)
Tunisian chamomile	Flower	10.80	(49)
Vanillosmopsis arborea	Stems	7.35	(50)

*No specified value; IC50 >X.

Table 2. Leishmanicidal activities of EOs against promastigotes of *Leishmania braziliensis*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Argyreia speciosa	Leaves	104.14	(57)
Citrus limon	Leaves	NSV*	(58)
Citrus sinensis	Leaves	NSV	(58)
Coriandrum sativum	Leaves	NSV	(58)
Cymbopogon citratus	Leaves	194.05	(58)
Lantana camara	Leaves	72.30	(52)
Mentha piperita	Leaves	NSV	(58)
Ocimum basilicum	Leaves	NSV	(58)
Origanum vulgare	Leaves	171.80	(58)
Piper aduncum	Leaves	77.90	(53)
Piper auritum	Leaves	52.10	(54)
Piper tuberculatum	Fruits	133.97	(59)
Rosmarinus officinalis	Leaves	NSV	(58)
Thymus vulgaris	Leaves	NSV	(58)
Zingiber officinale	Leaves	303.00	(58)

*No specified value; IC50 > X.

Table 3. Leishmanicidal activities of EOs against promastigotes of *Leishmania chagasi*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Copaifera reticulata	Seeds	7.88	(62)
Coriandrum sativum	Seeds	181.00	(62)
Croton cajucara	Leaves	66.70	(63)
Cymbopogon citratus	Leaves	45.00	(64)
Lippia alba	Aerial parts	18.90	(65)
Lippia citriodora	Aerial parts	5.20	(65)
Lippia dulcis	Aerial parts	37.10	(65)
Lippia gracilis (LGRA-106)	Leaves	86.32	(66)
Lippia gracilis (LGRA-110)	Leaves	77.26	(66)
Lippia idoides	Leaves	89.00	(64)
Lippia micromera	Aerial parts	51.80	(65)
Lippia origanoides	Aerial parts	4.40	(65)
Lippia sidoides	Seeds	19.76	(62)
Ocimum gratissimum	Leaves	75.00	(64)

In the new world, visceral leishmaniasis is associated with *L. Chagasi* (60). As details show, IC50 of 3 EOs, including *Copaifera reticulate, Lippia citriodora,* and *Lippia origanoides,* are around 5 µg.mL^{-1}. These EOs are suitable candidates for in-vivo studies.

A fatal form of leishmaniasis is visceral, in which parasite affects internal organs such as the spleen, liver, and bone marrow (61).

Table 4 shows the leishmanicidal potency of eight EOs on *L. donovani.* In India and West Africa, *L. donovani* is

Table 4. Leishmanicidal activities of EOs against promastigotes of *Leishmania donovani*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Artemisia annua	Leaves	14.60	(68)
Baccharis dracunculifolia	Leaves	42.00	(70)
Mentha piperita	N/A	50.00	(71)
Ocimum basilicum Mesten	Steam	49.60	(72)
Ocimum basilicum German	Steam	48.30	(72)
Ocimum sanctum	Steam	37.30	(72)
Piper auritum	Leaves	12.80	(54)
Syzygium aromaticum	Flower buds	21.00	(69)

the causative agent of visceral leishmaniasis (Kala-azar) (67). Among the reported IC50s, EOs of *Artemisia annua, Piper auritum,* and *Syzygium aromaticum* with values of 14.60, 12.80, and 21.00 µg.mL^{-1} respectively, were more effective than others (54,68,69).

In Table 5, IC50 of some EOs on *L. infantum* are summarized. *L. infantum* infection (causes of visceral leishmaniasis) is endemic in Southern Europe (73). LCA of *Nectandra hihua* and *Thymus hirtus* EOs with IC50 of 0.20 and 0.25 µg.mL^{-1} were very phantasies (36,74).

Results of LCA of some medicinal plants on *L. major* are summarized in Table 6. *L. major* and *L. tropica* in the old world are responsible for cutaneous leishmaniasis (7). Interestingly 3 documented IC50s were around 1 µg.mL^{-1}; those values were related to EOs of *Mentha pulegium, Rosmarinus officinalis,* and *Thymus hirtus.*

Table 7 summarizes the effect of many EOs on *L. mexicana,* which is one of the primary causes of cutaneous

Table 5. Leishmanicidal activities of EOs against promastigotes of *Leishmani infantum*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Artemisia campestris	Leaves/ stems	44.00	(75)
Artemisia herba-alba	Leaves/ stems	68.00	(75)
Cymbopogon citratus	Aerial parts	25.00	(76)
Guatteria australis	Leaves	30.71	(77)
Nectandra amazonum	Leaves	31.90	(36)
Nectandra gardneri	Leaves	2.70	(36)
Nectandra hihua	Leaves	0.20	(36)
Nectandra megapotamica	Leaves	12.50	(36)
Nigella sativa	Seeds	11.70	(78)
Piper aduncum	Leaves	32.50	(40)
Piper ossanum	Leaves	32.50	(40)
Piper tuberculatum	Fruits	143.59	(59)
Pulicaria vulgaris	Aerial parts	233.60	(79)
Thymus capitellatus	Aerial parts	37.00	(80)
Thymus hirtus	N/A	0.25	(74)
Tunisian chamomile	Flower	10.40	(49)
Vernonia polyanthes	Leaves	19.40	(81)

Table 6. Leishmanicidal activities of EOs against promastigotes of *Leishmania major*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Anise	Commercial	286.10	(82)
Balmmint	Commercial	7.00	(82)
Citrus limon	Leaves	231.40	(58)
Citrus sinensis	Leaves	NSV*	(58)
Clove	Commercial	58.40	(82)
Coriandrum sativum	Leaves	NSV	(58)
Cymbopogon citratus	Leaves	149.10	(58)
Cymbopogon citratus	Aerial parts	38.00	(76)
Dwarf Pine	Commercial	111.80	(82)
Konuka	Commercial	26.20	(82)
Lavandula angustifolia	N/A	110.00	(83)
Manuka	Commercial	208.10	(82)
Mentha pulegium	Aerial parts	1.30	(84)
Ocimum basilicum	Leaves	315.55	(58)
Origanum vulgare	Leaves	NSV	(58)
Peppermint	Commercial	227.50	(82)
Pine	Commercial	123.20	(82)
Piper auritum	Leaves	29.10	(54)
Pulicaria vulgaris	Aerial parts	244.70	(79)
Rosemary	Commercial	282.10	(82)
Rosmarinus officinalis	Aerial parts	1.20	(84)
Rosmarinus officinalis	Leaves	NSV	(58)
Rosmarinus officinalis	N/A	260.00	(83)
Satureja bakhtiarica	Leaves	150.00	(85)
Spruce	Commercial	29.90	(82)
Tea Tree	Commercial	403.00	(82)
Thyme	Commercial	127.40	(82)
Thymus capitellatus	Aerial parts	62.00	(80)
Thymus hirtus	N/A	0.43	(74)
Thymus vulgaris	Leaves	NSV	(58)
Zingiber officinale	Leaves	256.95	(58)

*No specified value; IC50 > X.

leishmaniasis in the New World (6). Between the reported IC50s (µg.mL^{-1}), EOs of *Cinnamomum cassia* (2.90) *Zingiber zerumbet* (3.30) and *Ocimum gratissimum* (4.80) were more effective than others (86).

Table 8 briefs the effect of 9 plant-derived EOs on *L. panamensis* promastigotes. Recently, it revealed that *L. panamensis* found in Central and South America, as well as it is the causative agent of the mucosal form (89). *Origanum vulgare* EO with IC50 of 42.23 µg.mL^{-1} was better than others (58).

Results of LCA of many EOs on promastigotes of *L. tropica* are given in Table 9. In the Middle East and North Africa, *L. tropica* and *L. major* are two main causative agents of human cutaneous leishmaniasis (7). Results demonstrated that 2 EOs, including *Myrtus communis* and *Nigella sativa* with IC50 of 8.40 and 9.30 µg.mL^{-1} respectively, were potent than others.

Table 7. Leishmanicidal activities of EOs against promastigotes of *Leishmania mexicana*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Amomum aromaticum	Fruits	9.20	(86)
Cinnamomum cassia	Stem barks	2.90	(86)
Elsholtzia ciliata	Leaves	8.40	(86)
Haplophyllum tuberculatum	Seed	16.00	(87)
Haplophyllum tuberculatum	Leave	16.60	(87)
Keetia leucantha	Leaves	20.90	(88)
Ocimum gratissimum	Leaves	4.80	(86)
Piper auritum	Leaves	63.30	(54)
Zingiber zerumbet	Rhizomes	3.30	(86)

Table 8. Leishmanicidal activities of EOs against promastigotes of *Leishmani panamensis*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Citrus limon	Leaves	NSV*	(58)
Citrus sinensis	Leaves	NSV	(58)
Coriandrum sativum	Leaves	427.95	(58)
Cymbopogon citratus	Leaves	180.83	(58)
Ocimum basilicum	Leaves	251.59	(58)
Origanum vulgare	Leaves	42.23	(58)
Rosmarinus officinalis	Leaves	NSV	(58)
Thymus vulgaris	Leaves	402.23	(58)
Zingiber officinale	Leaves	154.83	(58)

*No specified value; IC50 > X.

Table 9. Leishmanicidal activities of EOs against promastigotes of *Leishmania tropica*

Plant name	Part(s) of use	IC50 (µg.mL^{-1})	References
Cymbopogon citratus	Aerial parts	52.00	(76)
Myrtus communis	Leaves	8.40	(90)
Nigella sativa	Seeds	9.30	(78)
Thymus capitellatus	Aerial parts	35.00	(80)
Zataria multiflora Boiss	Aerial parts	89.30	(91)

In Tables 1-9, 179 IC50s of EOs on promastigotes of 9 types of *Leishmania* were gathered. The documented IC50s (µg.mL^{-1}) have been categorized as follow: IC50 <1: 6 EOs, IC50 1-10: 29 EOs, 10-100: 79 EOs, 100-500: 40 EOs, and no specified value (NSV): 25 EOs (i.e., IC50 < X). LCA of 24 EOs has been examined against at least 2 species of *Leishmania*. However, just LCA of 2 EOs on targeted promastigotes was under 10 µg.mL^{-1} simultaneously; *Thymus hirtus* EO with IC50s of 0.25 and 0.43 against *L. infantum* and *L. major*, respectively (74).

Besides, EO of *Nectandra gardneri* was also showed good LCA on *L. amazonensis* (2.1 μg.mL^{-1}) and *L. infantum* (2.7 μg.mL^{-1}) (36).

Interestingly, some EOs showed excellent LCA on one type of promastigotes, while its efficiency on an/other species was not acceptable. For instance, EO of *Ocimum gratissimum* was demonstrated substantial IC50s against *L. mexicana* (4.80 μg.mL^{-1}) (86), *L. chagasi* (75.00 μg.mL^{-1}) (64), and *L. amazonensis* (135 μg.mL^{-1}) (38). Also, *Nectandra megapotamica* EO against *L. amazonensis* and *L. infantum* was indicated different IC50s (μg.mL^{-1}), including 6.66 (37) and 12.50 (36), respectively.

Furthermore, IC50 of *Coriandrum sativum* EO on *L. amazonensis* and *L. chagasi* was reported as 19.10 μg.mL^{-1} (30) and 181.00 μg.mL^{-1} (62), respectively, while this value for *L. panamensis* was achieved at 427.95 μg.mL^{-1} (58). Besides, IC50s for *Piper auritum* EO against *L. donovani*, *L. major*, *L. braziliensis*, and *L. mexicana* were reported at 12.80, 29.10, 52.10, and 63.30 μg.mL^{-1}, respectively (54). Based on the results, it can be said that the LCA of EOs against different species is selective.

Conclusion

The articles published over the last 20 years on the leishmanicidal activity of EOs have been systematically reviewed. IC50s of 179 EOs on promastigotes of 9 different species of *Leishmania* were also documented, separately. Interestingly, thirty-five of IC50 values were lower than 10 μg.mL^{-1}, thus could be introduced for further investigations such as preparation of nano/formulations, performing in-vivo studies, and clinical trials. However, given the selective properties of EOs, their combination can lead to good results. In other words, depending on the endemic leishmaniasis, EOs can be combined and formulated as multifunctional drugs. In addition, the categorized results in this research would be an excellent guide for other researchers to select proper EOs.

Authors' contributions

SNG contributed to the extraction of information from literature and providing of information on leishmaniasis. NS contributed in extraction of information from literature and providing of information on information about EOs. The idea of doing this research as well as writing the manuscript done by MO. All authors read and approved the final report.

Conflict of interests

There is no conflict of interest to declare.

Ethical considerations

Ethical issues have been observed by the authors.

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