The leishmanicidal activity of essential oils: A systematic review

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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. Overall, 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.

Implecation 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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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 not 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 lifelong scars and severe disability or stigma (55,56).

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

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### 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 ambrosioides*    | (After IP treatment) | 6.71                  | (27)       |
| *Chenopodium ambrosioides*    | (After O treatment) | 5.55                  | (27)       |
| *Chenopodium ambrosioides*    | (wild type)    | 3.74                   | (27)       |
| *Chenopodium ambrosioides*    | N/A            | 3.70                   | (28)       |
| *Cinnamomum camphora*         | Leaves/ stems  | 54.00                  | (25)       |
| *Cinnamomum zeylanicum*       | Leaves         | NSV                    | (25)       |
| *Cordia verbeneae*            | 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)       |
| 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)       |
| Gaultheria 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)       |
| Myrocrodore urundeuva   | Leaves        | 205.00         | (35)       |
| Myrocyon 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 arboreatum        | 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 mikananum         | Leaves        | NSV            | (41)       |
| Piper mosenii           | Leaves        | 17.40          | (41)       |
| Piper ossanum           | Leaves        | NSV            | (40)       |
| Piper rivinoides        | Leaves        | 10.90          | (41)       |
| Piper xyloliseoides     | Leaves        | NSV            | (41)       |
| Pluchea carolinensis    | Leaves        | 24.70          | (45)       |
| Protium ovatum          | Leaves        | 2.280          | (46)       |
| Salvia scabra           | 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 arboarea | 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)       |
| *Origaniun 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 coajucara*        | 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 reticulata, 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 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 leishmaniasis.
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 was under 10 µg.mL⁻¹ respectively; LCA of 24 EOs has been examined against 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 IC50 of 0.25 and 0.43 against L. infantum and L. major, respectively (74).

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)       |
| Balm mint  | 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 officinalis | Leaves | 256.95        | (58)       |

*No specified value; IC50 > X.

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 | Leaf         | 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 Leishmania 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        | 402.23         | (58)       |
| Thymus vulgaris                | 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)       |
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 other species was not acceptable. For instance, EO of *Ocimum gratissimum* (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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