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Review

Systematic review on medicinal plants used for the treatment of *Giardia* infection

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ABSTRACT

Background: However, broad adoption of herbal remedies for giardiasis is at present hampered by uncertain findings of investigation not always sufficiently powered. This study was aimed at systematically reviewing the existing literature in herbal medicines to treat giardiasis.
Methods: This review was carried out 06- PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-Analysis Facility (SyRF) database. The search was performed in five databases which are Scopus, PubMed, Web of Science, EMBASE, and Google Scholar without time limitation for all published articles (*in vitro, in vivo*, and clinical studies). The searched words and terms were: "*Giardia*", "giardiasis", "extract", "essential oil", "herbal medicines", "anti-*Giardia*", "*In vitro*", "*In vivo*", "clinical trial" etc.
Results: Out of 1585 papers, 40 papers including 28 *in vitro* (70.0%), 7 *in vivo* (17.5%), 2 *in vitro/ in vivo* (5.0%), and 3 clinical trials (7.5%) up to 2020, met the inclusion criteria for discussion in this systematic review. The most widely used medicinal plants against *Giardia* infection belong to the family Lamiaceae (30.0%) followed by Asteraceae (13.5%), Apiaceae (10.5%). The most common parts used in the studies were aerial parts (45.0%) followed by leaves (27.4%) and seeds (7.5%). The aqueous extract (30.0%), essential oil (25.4%) and hydroalcholic and methanolic (10.5%) were considered as the desired approaches of herbal extraction, respectively.
Conclusion: The current review showed that the plant-based anti-*Giardia* agents are very promising as an alternative and complementary resource for treating giardiasis since had low significant toxicity. However, more studies are required to elucidate this conclusion, especially in clinical systems.

Contents

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1. Introduction

Giardiasis is considered as one of the most prevalent protozoan infection of humans in the worldwide which caused by an intestinal protozoan flagellate called Giardia lamblia (syn. G. duodenalis, G. intestinalis) (Plutzer et al., 2010). According to the World Health Organization (WHO) reports over 200 million recent cases of giardiasis that are diagnosed around the world every year; where it has been classified in the "neglected diseases initiative" (Plutzer et al., 2010). Previous reviews have showed that the infection rate in asymptomatic people varies from 8 to 30% in developing countries; while in industrialized countries the prevalence rate is 1–8% (Savioli et al., 2006). Humans especially children are usually infected as fecal-oral routes via direct or indirect the ingestion of infectious cysts in water and food. The incubation period varies from 9 to 15 days after ingestion of cysts (Feng and Xiao, 2011). Symptoms of this infection are varied from the absence of symptoms to acute watery diarrhea, nausea, epigastric pain and weight loss (Muhsen and Levine, 2012).

Since there is no effective and safe vaccine to prevent *Giardia* infection; therefore, chemotherapy with synthetic drugs is now considered as the best choice for giardiasis treatment (Watkins and Eckmann, 2014). In recent years, studies showed that the use of these synthetic drugs are associated with some limitations such as treatment-refractory cases and some drug-related side effects including nausea, mild headache, dizziness and a metallic taste in the mouth, yellowing of the skin and elevated liver enzymes (Watkins and Eckmann, 2014; Leitsch, 2015; Lalle and Hanevik, 2018); therefore, the search and discovery of new alternative anti-*Giardia* drugs with high effectiveness as well as minimal toxicity has been considered by researchers in recent years.

From ancient times, medicinal herbs and their derivatives have been broadly used for health promotion and therapy for chronic, as opposed to life-threatening, diseases (Lalle and Hanevik, 2018). Herbal medicines have also been successfully used in the treatment of a wide range of bacterial, viral, fungal, and parasitic infections (Vandana et al., 2012). Previous reviews have demonstrated the anti-*Giardia* effects of some herbal extract such as *Carum copticum, Lavandula stoechas, Tanacetum parthenium, Ferula assa-foetida, Allium paradoxum, Allium sativum, Artemisia annua, Allium ascalonicum, Chenopodium botrys, ZizIphora clinopodioides, Zataria multiflorahad, Eucalyptus globulus, Lippia beriandievi, Punica granatum*, they also reported that the hydroalcoholic extract of *Ferula assa-foetida*, *Chenopodium botrys*, and *Tanacetum parthenium* have the 100% *in vitro* efficacy against *G. lamblia*; while, the maximum *in vivo* efficacy against giardiasis was observed for the *Allium sativum* extract at the concentration of 80 mg/mL (Hezarjaribi et al., 2015; Bahmani et al., 2014; Nazer et al., 2019). However, broad adoption of herbal remedies for giardiasis is at present hampered by uncertain findings of investigation not always sufficiently powered. This study aimed at systematically reviewing the existing literature in herbal medicines to treat giardiasis.

2. Materials and methods

2.1. Search strategy

This review was carried out 06- PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-Analysis Facility (SyRF) database. In this review study, data were obtained from published articles indexed in multiple databases such as Scopus, PubMed, Web of Science, EMBASE, and Other database like Google Scholar. We interrogated these databases for scientific articles that related to anti-Giardia effects of medicinal without a date limitation. Thus, all published studies *in vitro*, *in vivo*, and clinical studies were identified. It included studies published in languages other than English in the searching process if they have an English abstract. These studies were retrieved using the search terms "*Giardia*", "giardiasis", "extract", "essential oil", "herbal medicines", "anti-*Giardia*", "*in vitro*", "*in vivo*", "clinical trial" (Fig. 1).

2.2. Quality assessment and article selection

Those studies were examined in which the effects of herbal medicines against giardiasis. First, the studies were imported to the EndNote X9 software (Thomson Reuters, New York, NY, USA) and duplicate studies were deleted. Afterwards, three independent authors examined the title and abstract of the studies and the relevant studies were included for further analysis. The same authors carefully read the studies and the eligible studies with adequate inclusion criteria were selected.

2.3. Exclusion criteria

The studies with inadequate information, abstract submitted in congresses whose full texts were not available, failure to match methods with results the incorrect interpretation of the results was excluded from the current study.

2.4. Inclusion criteria

Inclusion criteria of this study were the articles testing the anti-*Giardia* effects of medicinal herbs against *Giardia* infection, emphasizing the *in vitro, in vivo*, and clinical trial studies (Fig. 1).

2.5. Data extraction

Three independent authors extracted information from the selected articles and, if needed, the differences were resolved by the corresponding author. The extracted data include plant name, family, part of used, extraction, dose, parasite form, results, reference.

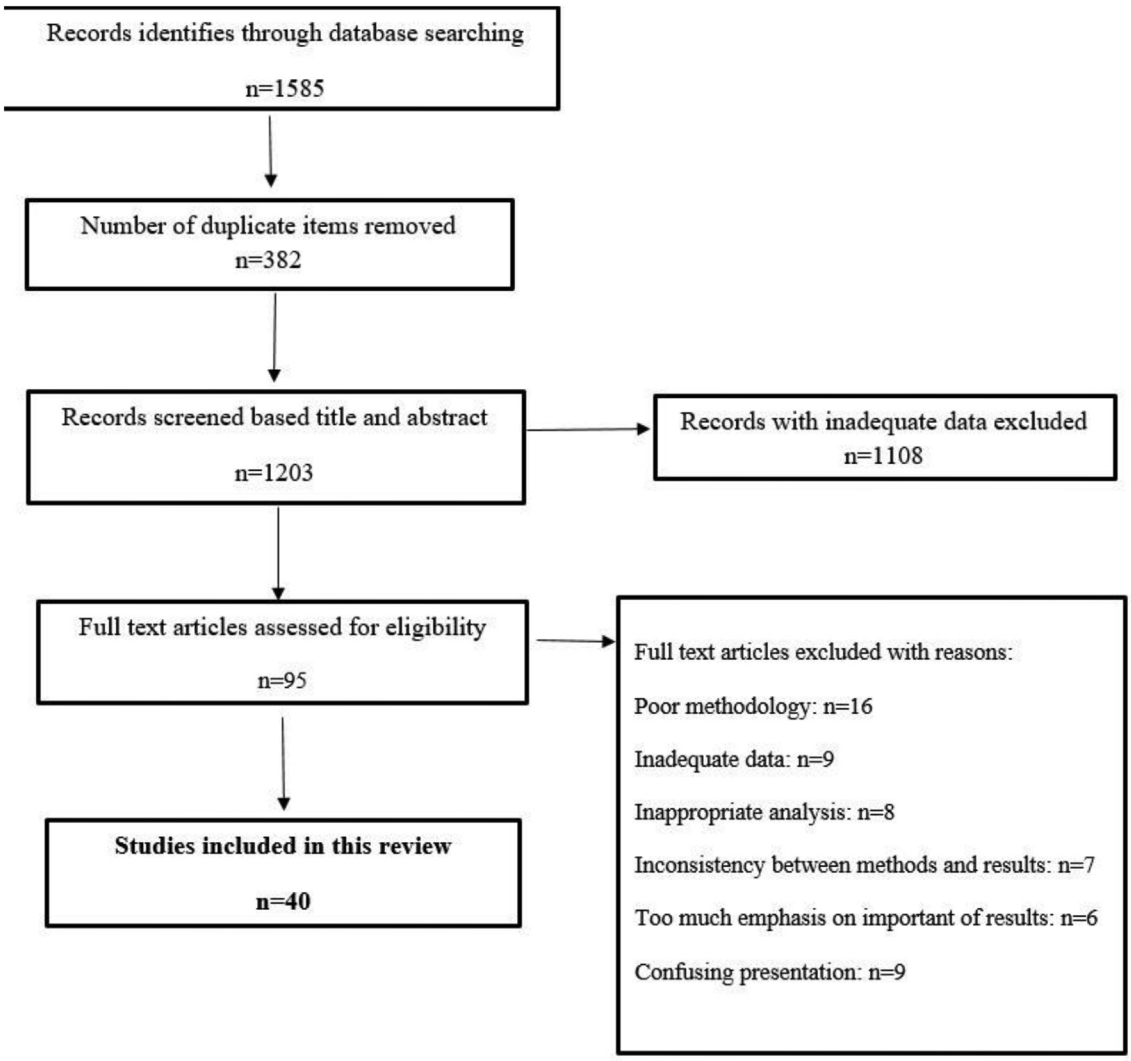

Fig. 1. Flowchart describing the study design process.

3. Results

Out of 1585 papers, 40 papers including 28 *in vitro* (70.0%), 7 *in vivo* (17.5%), 2 *in vitro/ in vivo* (5.0%), and 3 clinical trials (7.5%) up to 2020, met the inclusion criteria for discussion in this systematic review with the data extracted presented in Tables 1–3. The obtained results showed 57 plant species, belonging to 48 genera and 19 families, which have pharmacological confirmation and therapeutic effects against *Giardia* infection (Tables 1–3 and Fig. 2). Totally 19 families were found the anti-*Giardia* activity *in vitro* and *in vivo*. The most widely used medicinal plants against *Giardia* infection belong to the family Lamiaceae (30.0%) followed by Asteraceae (13.5%) and Apiaceae (10.5%) (Fig. 3).

The obtained results showed that the most common parts used in the studies were aerial parts (45.0%) followed by leaves (27.4%) and seeds (7.5%). Whereas, other parts used were flowers, peels, bulb, and fruits (Fig. 4). The findings of the present review showed that aqueous extract (30.0%), essential oil (25.4%) and hydroalcholic and methanolic (10.5%) were considered as the desired approaches of herbal extraction, whereas the chloroformic (10.7%) and petroleum ether extract (7.5%) were the second most used herbal extractions (Fig. 5).

Based on the obtained results demonstrated that the most effective medicinal plants against *G. lamblia in vitro* were *A. sativum, Artemisia sieberi, and Chenopodium botrys* which showed the greatest effect at a concentration of 0.1 μg/mL. *In vivo* studies also demonstrated that the most effective medicinal herbs against animal model giardiasis was *Helianthemum glomeratum* metanolic extract with the ED_{50} value of 0.125 mg/kg. By clinical studies, aqueous extract of *Anethum graveolens* at the dose of 1 ml/tree times for 5 days, significantly improved the symptoms in pediatric patients with giardiasis; whereas the extract was safe and tolerable over treatment way. *Triticum vulgare* and *Mentha crispa* at the dose of 2 g/day for 7 and 10 days considerably reduced both cyst passage and copro-antigen levels in asymptomatic and symptomatic patients with giardiasis compared with the placebo group.

4. Discussion

Based on WHO reports (2005), medicines herbs and plant-derived compounds due to minimal or no industrial processing and side effects have been widely applied to treat not only on infectious diseases but also on a wide range of other diseases such as cardiovascular, gastrointestinal, diabetes, cancer through local or regional healing approaches in developing and developed countries (World Health Organization, 2005). Today, it has been proven that biological activity and beneficial medicinal possessions of medicinal herbs is because of having the secondary metabolites

Table 1
A list of medicinal herbs with *in vitro* anti-*Giardia* effects. From 40 papers which met the inclusion criteria for based on the 06- PRISMA guideline, 28 papers (70.0%) including 37 genera and 48 species of plants showed the anti-*Giardia* activity *in vitro*.

Plant name	Family	Part of used	Extraction	Collection place	Dose	Parasite form	Results	Year	Ref.
Achillea santolina	Asteraceae	Aerial parts	Aqueous extract	Iraq	31.25–2000 mg/ml	Trophozoite	The results showed that at the dose of 2000 mg/ml completely eliminate the G. lamblia trophozoites.	2010	(Al-kaissi, 2010)
Ageratum conyzoides	Asteraceae	Flower, leaf,	Essential oil-Hydroalcholic extract	Thailand	100–1000 μg/mL	Trophozoite	White–purple leave and flower purple extracts showed high activity (IC50 ≤ 100 μg/mL) against *G. duodenalis* trophozoites, with IC50 ± SD values of 45.67 ± 0.51 and 96.00 ± 0.46 μg/mL, respectively. In subsequent experiments, IC50 ± SD values of LW–P and FP essential oils were 35.00 ± 0.50 and 89.33 ± 0.41 μg/mL, respectively. TEM revealed the degeneration of flagella and ventral discs of G. duodenalis trophozoites following exposure to crude extracts.	2020	(Pintong et al., 2020)
Allium sativum	Amaryllidaceae	Aerial parts	Essential oil	Iran	0.2, 0.1, 0.01 and 0.001 μg/mL	Trophozoite-cyst	The essential oil at the concentration of 0.1 and 0.2 μg/mL indicated appreciate parasiticidal effect ($p < 0.05$).	2020	(Azadbakht et al., 2020)
Allium sativum	Amaryllidaceae	Bulb	Hydroalcoholic extracts	Iran	2 and 5 mg/ml	Cyst	The fatality rate on G. lamblia cysts *in vitro* was 22.65 ± 10.47%.	2016	(Fallahi et al., 2016)
Artemisia annua	Asteraceae	Aerial parts	Hydroalcholic extract	Iran	100 mg/ml	Cyst	Results of this study indicated that concentration of 50 and 100 mg/ml of hydroalcholic extracted of A. annua after 3 and 24 h has the most killing and cytotoxicity activity on G. lamblia cysts *in vitro*.	2020	(Bahman et al., 2012)
Artemisia annua	Asteraceae	Aerial parts	Chloroformic extract	Iran	1, 10, 50 and 100 mg/ml	Trophozoite cyst	Cyst and trophozoite contact (intermix) of *G. lamblia* with extract of *A. annua* with variant concentrations (1, 10, 50 and 100 mg/ml) after 1 and 180 min caused following cyst and trophozoite elimination rates: (67, 69, 71 and 73%), (65, 67, 67 and 72%), (94, 96, 97 and 99%) and (100, 100, 100 and 100%), respectively.	2016	(Golami et al., 2016)
Artemisia annua	Asteraceae	Leave	Chloroformic extract	Iran	1, 10, 50 and 100 mg/ml	Cyst trophozoite	Chloroformic extracts of A. annua at 10 mg/ml and 100 mg/ml concentration had affected on Giardia cyst 96%, 99% and trophozoit (100%) after 3 h.	2014	(Gholami et al., 2014)
Artemisia campestris	Asteraceae	Aerial parts	Aqueous extract	Iraq	31.25–2000 mg/ml	Trophozoite	The results showed that at the dose of 2000 mg/ml completely eliminate the G. lamblia trophozoites.	2010	(Al-kaissi, 2010)
Artemisia sieberi	Asteraceae	Aerial parts	Essential oil	Iran	0.2, 0.1, 0.01 and 0.001 μg/mL	Trophozoite-cyst	The essential oil at the concentration of 0.1 and 0.2 μg/mL indicated appreciate parasiticidal effect ($p < 0.05$).	2020	(Azadbakht et al., 2020)
Carum copticum	Apiaceae	Leaves	Aqueous extract, essential	Iran	1–100 mg/ml	Cyst	After 60 min Minimum Inhibitory Concentrations (MIC) of *Carum copticum* alcoholic extracts and essential oil were 100 mg and 8 mg/ml, respectively. After 120 min, MIC of *Carum copticum* alcoholic extracts and essential oil were 75 mg and 6 mg/ml, respectively; and after 180 min MIC of *Carum copticum* alcoholic extracts and essential oil were 75 and 4 mg/ml, respectively.	2009	(Shahabi et al., 2009)
Chenopodium botrys	Chenopodiaceae	Aerial parts	Essential oil	Iran	0.2, 0.1, 0.01 and 0.001 μg/mL	Trophozoite/cyst	The essential oil at the concentration of 0.1 and 0.2 μg/mL indicated appreciate parasiticidal effect ($p < 0.05$).	2016	(Fallahi et al., 2016)
Chenopodium botrys	Chenopodiaceae	Seed	Aqueous and alcoholic extracts	Iran	1.25, 2.5,5,10 and 20 mg/ml	Cyst	The highest giardicidal effect of alcoholic and aqueous extracts of Chenopodium botrys L. at 37 °C, in 20 mg/ml and 5 h after experiment were 100% and 66.1% respectively.	2013	(Rezaeemanesh et al., 2013)
Citrus aurantifolia	Rutaceae	Peels	Hexane extract	México	1–10 mg/mL.	Trophozoite	4-hexen-3-one, citral and geraniol showed IC_{50} values of 34.2, 64.5 and 229.49 μg/ml in axenic cultures after 24 hr of incubation, respectively. When these results were compared with a positive control of metronidazole; 4-hexen-3-one was 66 times; citral was 112 and geraniol was 441 times less active respectively. The other tested compounds did not inhibit the growth of cultured *G. lamblia* trophozoites.	2015	(Domínguez-Vigil et al., 2015)
Cucurbita pepo L,	Cucurbitaceae	Seed	Petroleum ether, and methanol.	Sudan	1000 ppm, 500 ppm, 250 ppm	trophozoite	C. pepo seeds petroleum ether extract exhibited 100% mortality within 120 h giving IC50 of 60671.32 ppm (with a concentration of 500 ppm).	2013	(Elhadi et al., 2013)

Table 1 (*continued*)

Plant name	Family	Part of used	Extraction	Collection place	Dose	Parasite form	Results	Year	Ref.
Cucurbita pepo L, Cucurbita maxima D	Cucurbitaceae	Seed	Petroleum ether, and methanol.	Sudan	1000 ppm, 500 ppm, 250 ppm	trophozoite	C. maxima seeds petroleum ether extract exhibited 100% mortality within 48 h giving IC50 of 548.80 ppm (with a concentration of 1000 and 500 ppm).	2013	(Elhadi et al., 2013)
Cuminum cyminum	Apiaceae	Aerial parts	Aqueous extract	Iraq	31.25–2000 mg/ml	Trophozoite	The results showed that at the dose of 2000 mg/ml reduce the viability of the G. lamblia trophozoites to 25%.	2010	(Al-kaissi, 2010)
Curcuma longa	Zingiberaceae	Stem bark	dichloromethane extracts	Egypt	1, 10 and 50 mg⁄mL	Cyst	The mortality (death) rate on Giardia cysts in was 85% after treatment with extract at concentration of 50 mg/mL after 60 min.	2016	(Dyab et al., 2016)
Cymbopogon citratus	Poaceae	Leaves	Aqueous extract	Egypt	500 mg/ml	Cyst	*C. citratus* aqueous extracts were effective against G. lamblia both *in vitro* and *in vivo* and they could be natural therapeutic alternative agents to MTZ.	2019	(Harba et al., 2019)
Echinophora cinerea	Apiaceae	Aerial parts	Aqueous xtract	Iran	4 and 8 mg/ml	Cyst	The findings showed, 4 and 8 mg/mL of the same extract caused the gradual destruction of G. lamblia cysts (7.92 and 7.89 cysts/h, respectively). Furthermore, the mean rate of cysts destruction was found to be 8.83 cysts/h by 8 mg/mL of *E. cinerea* extract.	2018	(Ezatpour et al., 2018)
Eucalyptus camaldulensis	Myrtaceae	Aerial parts	Aqueous extract	Iraq	31.25–2000 mg/ml	Trophozoite	The results showed that at the dose of 2000 mg/ml completely eliminate the G. lamblia trophozoites.	2010	(Al-kaissi, 2010)
Eucalyptus globulus	Myrtaceae	Aerial parts	Essential oil	Iran	0.2, 0.1, 0.01 and 0.001 μg/mL	Trophozoite-cyst	The essential oil at the concentration of 0.1 and 0.2 μg/mL indicated appreciate parasiticidal effect ($p < 0.05$).	2020	(Azadbakht et al., 2020)
Eucalyptus radiata	Myrtaceae	Leaves	Methanol extract	Iran	10, 100, 200 mg/ml	Cyst	The methanol extracts with the dilution of 200 mg/ml in 60 mins have the fatality effect of 63.3%.	2012	(Safarnezhad Tameshkel et al., 2012)
Ferula assa-foetida	Apiaceae	Aerial parts	Aqueous and ethanolic extract	Iran	1, 1.25, 25, 5, 10, and 20 mg/ml	Cyst	The highest effect of ethanol extract was 100% at 20 mg/ml and in the 4th hour after experiment, while the maximum effect of aqueous extract was 57.23% at the same temperature and with the same concentration, in the 5th hour.	2012	(Rezaiemanesh and Shirbazou, 2012)
Ferula-asa-feotida	Apiaceae	Aerial parts	Essential oil	Iran	10–500 mg/ml	Cyst	This study determined some plant essential oils have benefit effect on Giardia cyst and are suitable for further study to make herbal remedy from them.	2003	(Nr et al., 2003)
Heracleum glabrescens	Apiaceae	Grain	Methanolic extract	Iran	10, 100, 200 mg/ml	Cyst	The methanol extracts with the dilution of 200 mg/ml in 60 mins have the fatality effect of 44%.	2012	(Safarnezhad Tameshkel et al., 2012)
Lagenaria siceraria	Cucurbitaceae	Seed	Petroleum ether, and methanol.	Sudan	1000 ppm, 500 ppm, 250 ppm	Trophozoite	L. siceraria petroleum ether extract exhibited 100% mortality within 72 h with IC50 of 95.65 ppm.	2013	(Elhadi et al., 2013)
Lavandula angustifolia	Lamiaceae	Aerial parts	Essential oil	Iran	1, 0.5 , 0.1%	Trophozoite	The results demonstrated that low (≤1%) concentrations of L. angustifolia oil can completely eliminate G. duodenalis.	2017	(Vazini, 2017)
Lavandula intermedia	Lamiaceae	Aerial parts	Essential oil	Iran	1, 0.5 , 0.1%	Trophozoite	The results demonstrated that low (≤1%) concentrations of L. × intermedia oil can completely eliminate G. duodenalis.	2017	(Vazini, 2017)
Lipia beriandieri	Verbenaceae	Aerial parts	Aqueous extract	México	1, 2, 5, 10 mg/ml	Trophozoite	The extract showed 90% mortality in trophozoites.	1994	(Ponce-Macotela et al., 1994)
Lippia graveolens	Verbenaceae	Aerial parts	Essential oil	Portugal	10–400μg/ml	Trophozoite	The IC50 value was 257 μg/ml. Considering morphoplogical changes, it was roundly shape, irregular dorsal and ventral surface, presence of membrane blebs, electrodense precipitates in cytoplasm and nuclei, and internalization of flagella and ventral disc.	2010	(Machado et al., 2010)
Mangifera indica	Anacardiaceae	Aerial parts	Aqueous extract	Iraq	31.25–2000 mg/ml	Trophozoite	The results showed that at the dose of 2000 mg/ml reduce the viability of the G. lamblia trophozoites to 75%.	2010	(Al-kaissi, 2010)
Mentha longifolia	Lamiaceae	Leaf	Chloroform extract	Egypt	25–200μg/ml	Trophozoite	Chloroform extract at the dose of 200 μg/ml inhibit > 20% of trophozoites.	2010	(El-Badry et al., 2010)
Mentha piperita	Lamiaceae	Leaves	Methanol, dichloro-methane and n-hexane extract	Brazil	1, 10, 50 and 100 μg/ml	Trophozoite	The aqueous extract showed no effect against the trophozoites with an IC50 > 100 μg/ml. The aqueous fraction presented a moderate activity with an IC50 of 45.5 μg/ml. The dichloromethane fraction showed the best antigiardial activity, with an IC50 of 0.75 μg/ml after 48 h of incubation. The morphological and adhesion assays showed that this fraction caused several alterations on plasma	2007	(Vidal et al., 2007)

(*continued on next page*)

Table 1 (*continued*)

Plant name	Family	Part of used	Extraction	Collection place	Dose	Parasite form	Results	Year	Ref.
							membrane surface of the parasite and inhibited the adhesion of G. lamblia trophozoites.		
Myrtus communis	Myrtaceae	Aerial parts	Essential oil	Iran	10–500 mg/ml	Cyst	This study determined some plant essential oils have benefit effect on Giardia cyst and are suitable for further study to make herbal remedy from them.	2003	(Nr et al., 2003)
Nigella sativa	Ranunculaceae	Seed	Ethanolic extract	Egypt	500 μg/ml	Trophozoite	The results exhibited 95% mortality within 96 h, at a concentration 500 μg/ml against *G. lamblia* trophozoites *in vitro*	2015	(Kabbashi et al., 2015)
Ocimum basilicum	Lamiaceae	Leaves	Petroleum ether, ethyl acetate, methanol and aqueous extract	Egypt	100 mg\ ml	Trophozoite	Pet. Ether extract (IC50 = 14.9 mg ml-1), Ethyl acetate extract (IC50 = 25.4 mg ml-1), methanol extract from O. basilicum (IC50 = 33.8 mg ml-1) had potent activity against *G. lamblia* (IC50 = 2.383 mg/ml).	2013	(Elbadr et al., 2013)
Ocimum basilicum	Lamiaceae	Leaf	Chloroform extract	Egypt	5–200 μg/ml	Trophozoite	Chloroform extract from *O. basilicum* was strongly active against G. duodenalis with IC50 = 53.31 μg/ml.	2010	(El-Badry et al., 2010)
Olea europaea	Oleaceae	Leave	Hydroalcoholic extracts	Iran	2 and 5 mg/ml	Cyst	The results demonstrated that olive leaf extract had the most fatality rate on G. lamblia cysts *in vitro* (37.90 ± 7.01%).	2016	(Fallahi et al., 2016)
Origanum virens	Lamiaceae	Aerial parts	Essential oil	Portugal	10–300 μg/ml	Trophozoite	The IC50 value was 85 μg/ml. Considering morphoplogical changes, it was roundly shape, irregular dorsal and ventral surface, presence of membrane blebs, electrodense precipitates in cytoplasm and nuclei, and internalization of flagella and ventral disc.	2010	(Machado et al., 2010)
Origanum vulgare	Lamiaceae	Flowering aerial parts	Hydroalcoholic extract	Iran	10, 100 and 200 mg/ml	Cyst	The results indicated anti-Giardia activity of OV hydroalcoholic extract and the best response was achieved at higher levels so that there were no significant differences among OV groups at levels of 200 mg/kg with metronidazole ($P > 0.05$	2018	(Davoodi and Abbasi-Maleki, 2018)
Pulicaria undulata	Asteraceae	Aerial parts	Aqueous extract	Egypt	200 mg/kg	Cyst	*P. undulata* aqueous extracts were effective against G. lamblia both *in vitro* and *in vivo* and they could be natural therapeutic alternative agents to MTZ.	2019	(Harba et al., 2019)
Pulsatilla chinensis	Ranunculaceae	Aerial parts	Ethyl acetate and aqueous extract	China	39.65–5,000 μg/ml	Trophozoite	The PWE and ethyl acetate extract inhibited G. intestinalis trophozoites adherence after 3 h of incubation and killed almost 50% of the parasite population in a time-dependent manner. Changes in morphology, presence of precipitates in the cytoplasm, dissolved cytoplasm with large vacuole, break of flagella and ventral disk, membrane blebs, and intracellular and nuclear clearance of the treated trophozoites were observed by scanning and transmission electron microscopy.	2012	(Li et al., 2012 1)
Rosmarinus officinalis	Lamiaceae	Leaves	Petroleum ether, ethyl acetate, methanol and aqueous extract	Egypt	100 mg\ ml	Trophozoite	Pet. Ether extract (IC50 = 4.382 mg ml-1), Ethyl acetate extract (IC50 = 2.02 mg/ml), and methanol extract (IC50 = 2.383 mg ml-1) from *R. officinalis* were strongly active against G. lamblia (IC50 = 2.383 mg/ml).	2013	(Elbadr et al., 2013)
Sambucus ebulus	Adoxaceae	Fruit	Aqueous Extract	Iran	1, 10, 50 100 mg/mL	Cyst	Considering excellent antigiardial activity of *S. ebulus in vitro*, it seems to have potential for the treatment of the parasitic disease caused by the protozoan G. lamblia.	2013	(Rahimi-Esboei et al., 2013)
Satureja hortensis	Lamiaceae	Leaves	Methanol extract	Iran	10, 100, 200 mg/ml	Cyst	The methanol extracts with the dilution of 200 mg/ml in 60 mins have the fatality effect of 84.3%.	2012	(Safarnezhad Tameshkel et al., 2012)
Satureja khuzestanica	Lamiaceae	Leaves	Hydroalcoholic extracts	Iran	2 and 5 mg/ml	Cyst	The fatality rate on G. lamblia cysts *in vitro* was 32.52 ± 9.07%.	2016	(Fallahi et al., 2016)
Stachys lavandulifolia	Lamiaceae	Leaves	Aqueous and n-hexane extract	Iran	2.5,5, 10,25,50 mg/mL	Cyst	The watery extract at the concentration of 100 mg/mL killed 93% of cysts after 6 h. The n-hexane extract at the concentration of 100 mg/mL killed 100% of cysts after 6 h. Both extracts showed dose dependent antigiardial activity and the n-hexane extract was better than the watery extract.	2017	(Barati et al., 2017)
Syzygium aromaticum	Myrtaceae	Leaves	Aqueous extract	Egypt	100 mg/mL	Trophozoite	*S. aromaticum* was good activity against G. lamblia (IC50 = 0.755 mg/mL).	2015	(Dahab, 2015)
Tanacetum parthenium	Asteraceae	Aerial	Chloroformic	Iran	1, 10, 50 and	Trophozoite-	The chloroformic extract of T. parthenium at 1 mg/ml and 10 mg/ml	2014	(Gholami et al.,

Table 1 (*continued*)

Plant name	Family	Part of used	Extraction	Collection place	Dose	Parasite form	Results	Year	Ref.
		parts	Extract		100 mg/ml	cyst	concentration killed 97%, 99% on cyst and at 1 mg/ml 100% on trophozite after 3 h, 50 mg/ml effected 100% trophozite after one hour, respectively.		2014)
Thymbra capitata	Lamiaceae	Aerial parts	Essential oil	Egypt	10–300μg/ml	Trophozoite	The IC50 value was 71 μg/ml. Considering morphoplogical changes, it was roundly shape, irregular dorsal and ventral surface, presenceof membrane blebs, electrodense precipitates in cytoplasmand nuclei, and internalization of flagella and ventral disc.	2016	(Abdel-Hafeez et al., 2016)
Thymus vulgarize,	Lamiaceae	Aerial parts	Essential oil	Iran	10–500 mg/ml	Cyst	This study determined some plant essential oils have benefit effect on Giardia cyst and are suitable for further study to make herbal remedy from them.	2012	(Rezaiemanesh and Shirbazou, 2012)
Thymus zygis	Lamiaceae	Aerial parts	Essential oil	Portugal	10–300 μg/ml	Trophozoite	The IC50 value was 185 μg/ml. Considering morphoplogical changes, it was roundly shape, irregular dorsal and ventral surface, presence of membrane blebs, electrodense precipitates in cytoplasm and nuclei, and internalization of flagella and ventral disc.	2010	(Machado et al., 2010)
Zataria multiflora	Lamiaceae	Aerial parts	Essential oil	Iran	10–500 mg/ml	Cyst	This study determined some plant essential oils have benefit effect on Giardia cyst and are suitable for further study to make herbal remedy from them.	2012	(Rezaiemanesh and Shirbazou, 2012)
Zatraria multiflora	Lamiaceae	Aerial parts	Essential oil	Iran	0.2, 0.1, 0.01 and 0.001 μg/mL	Trophozoite-cyst	The essential oil at the concentration of 0.1 and 0.2 μg/mL indicated appreciate parasiticidal effect ($p < 0.05$).	2020	(Azadbakht et al., 2020)
Zingiber officinale	Zingiberaceae	Root	Aqueous extract	Egypt	20 mg/ml.	Trophozoite	The present study confirmed that ginger extract is equally active against *G. lamblia* as NTZ. Moreover, this simple *G. lamblia* axenic culture medium proved beneficial for evaluation of the susceptibility of isolates to antiparasitic drugs	2016	(Abdel-Hafeez et al., 2016)
Zingiber officinale	Zingiberaceae	Rhizome	dichloromethane extracts	Egypt	1, 10 and 50 mg/mL	Cyst	The mortality (death) rate on Giardia cysts in was 97% after treatment with extract at concentration of 50 mg/mL after 60 min.	2016	(Dyab et al., 2016)

Table 2
A list of *in vivo* studies considering anti-*Giardia* effects some medicinal herbs. From 40 papers which met the inclusion criteria for based on the 06- PRISMA guideline, 7 *in vivo* (17.5%) and 2 *in vitro/ in vivo* (5.0%) up to 2020, met the inclusion criteria for discussion in this systematic review.

Plant name	Family	Part of used	Extraction	Collection place	Dose	Conditions	Parasite	Results	Year	Ref.
Allium paradoxum	Amaryllidaceae	Leave	Hydroalcoholic extracts	Iran	20, 50, 100 mg/ml	*In vivo* (Balb/c mice)	Cyst	At the dose of 100 mg/ml is able to remove the G. lamblia cysts. This effect is significant compared to the control group ($P < 0.05$).	2014	(Elmi et al., 2014)
Allium sativum	Amaryllidaceae	Bulb	Chloroform extract	Iran	80 mg/ml	*In vivo* (Balb/ c mice)	Cyst	The cysts of *G. lamblia* were more sensitive to garlic extract than *G. muris*. Although, the infected mice in the test groups were not cured by the doses of 20 and 40 mg/kg body weight, they were completely cyst-free with the dose of 80 mg/kg within three days.	2006	(Safar Harandi et al., 2006)
Curcuma longa	Zingiberaceae	Stem bark	dichloromethane extracts	Egypt	10 and 20 mg/ kg/day	*In vivo* (Balb/c mice)	Cyst	The administration of curcumin especially at the dose 20 mg/ kg/day significantly reduced the excretion rates of dead cysts and intestinal trophozoite (84.7%) in the faeces of the treated groups.	2016	(Dyab et al., 2016)
Cymbopogon citratus	Poaceae	Leaves	Aqueous extract	Egypt	500 mg/kg	*In vivo* (Albino mice)	Cyst	*C. citratus* aqueous extracts were effective against G. lamblia both *in vitro* and *in vivo* and they could be natural therapeutic alternative agents to MTZ.	2019	(Harba et al., 2019)
Helianthemum glomeratum	Cistaceae	Flower	Metanolic extract	Mexico	1.25, 2.5, 5, 10 and 20 mg /kg	*In vivo* (CD-1 mice)	Trophozoite	The ED50 (mg/kg) obtained was 0.125 mg/kg. The extract was four times more active than the extract of Rubus coriifolius, and its activity is comparable to metronidazole and emetine	2016	(Barbosa et al., 2006)
Lavandula angustifolia	Lamiaceae	Aerial parts	Aqueous extract	Australia	100,200, 400 ml/mg	*In vivo* (Souri mice)	Cyst	The results of the current study indicated that Lavandula angustifolia has conceivable effects *in vivo* and it will be a suitable alternative for treatment of Giardiasis.	2006	(Moon et al., 2006 1)
Lavandula stoechas	Lamiaceae	Aerial parts	Hydroalcoholic extract	Iran	100, 200, and 400 mg/ml for 10 days	*In vivo* (Swiss albino mice)	Cyst	The extract significantly reduced the excretion rates of cysts 95.1, 84.3, and 77.7% after treatment with 400, 200, and mg/ml for 10 days	2017	(Vazini, 2017)
Pulicaria undulata	Asteraceae	Aerial parts	Aqueous extract	Egypt	200 mg/kg	*In vivo*	Cyst	*P. undulata* aqueous extracts were effective against G. lamblia both *in vitro* and *in vivo* and they could be natural therapeutic alternative agents to MTZ.	2019	(Harba et al., 2019)
Punica granatum	Punicaceae	Peel	Methanolic extract	Saudi Arabia	300 mg/ kg/day for 30 days	*In vivo* (Swiss albino mice)	Cyst	Results revealed that the prevention rate in the experimental groups reached approximately 50% by the 10th day of using pomegranate peel extract. Moreover, stool cyst counts of groups showed a significant reduction in the shedding of cysts approximately 75.6% by day 20 post-infection.	2017	(Al-Megrin, 2017)
Rubus coriifolius	Rosaceae	Fruits	Methanolic extract	Australia	1.25, 2.5, 5, 10 and 20 mg /kg	*In vivo* (CD-1 mice)	Trophozoite	The methanolic extracts showed antigiardial activity with ED50 (mg/kg) obtained was 0.506 mg/kg.	2006	(Moon et al., 2006 1)
Yucca baccata	Asparagaceae	Stem	Aqueous extract	Mexico	24.4, 12.2, and 6.1 mg/ mL/day for 3 days	*In vivo* (Mongolian gerbils)	Trophozoites	Yucca extracts reduced, albeit not significantly, the trophozoite counts in the duodenum segment. Only the high-extract concentration significantly reduced the trophozoite counts in the proximal segment and it was similar to that of metronidazole	2014	(Quihui-Cota et al., 2014)
Zingiber officinale	Zingiberaceae	Rhizome	dichloromethane extracts	Egypt	10 and 20 mg/ kg/day	*In vivo* (Balb/c mice)	Cyst	The administration of ginger especially at the dose 20 mg/kg/day significantly reduced the excretion rates of dead cysts and intestinal trophozoite (100%) in the faeces of the treated groups similar to that of the 20 mg/kg/day MTZ treatment.	2016	(Dyab et al., 2016)

Table 3
A list of clinical trial studies considering anti-*Giardia* effects some medicinal herbs. From 40 papers which met the inclusion criteria for based on the 06- PRISMA guideline, 3 clinical trials (7.5%) up to 2020, met the inclusion criteria for discussion in this systematic review.

Plant name	Family	Part of used	Extraction	Collection place	Dose	Parasite	Results	Year	Ref.
Anethum graveolens	Apiaceae	Leave	Aqueous extract	Iraq	1 ml 3 times a day for 5 days	Trophozoite-cysts	This study showed that pediatric patients with giardiasis may benefit from 5 days treatment with AGAE administered as 1 ml 3 times daily, the improvement in the symptom with this herbal agent was comparable to the standard pharmacological agent Met; results showed that AG is safe and tolerable over treatment course.	2014	(Sahib et al., 2014)
Mentha crispa	Lamiaceae	Leave	Aqueous extract	Brazil	2 g/day for 10 days	Cyst	Results showed that the cure rate for the Secnidazole group (84.0%) was significantly higher (P = 0.0002) as that verified in the M. crispa group (47.83%).	2011	(Teles et al., 2011)
Triticum Vulgare (Wheat)	Poaceae	Germ	Oil	Canada	2 g, 3 times a day for 7 days	Cyst	In asymptomatic and symptomatic subjects, both cyst passage and coproantigen levels were significantly reduced in those taking WG compared with the placebo group (P < 0.01 and P = 0.06, respectively).	2001	(Grant et al., 2001)

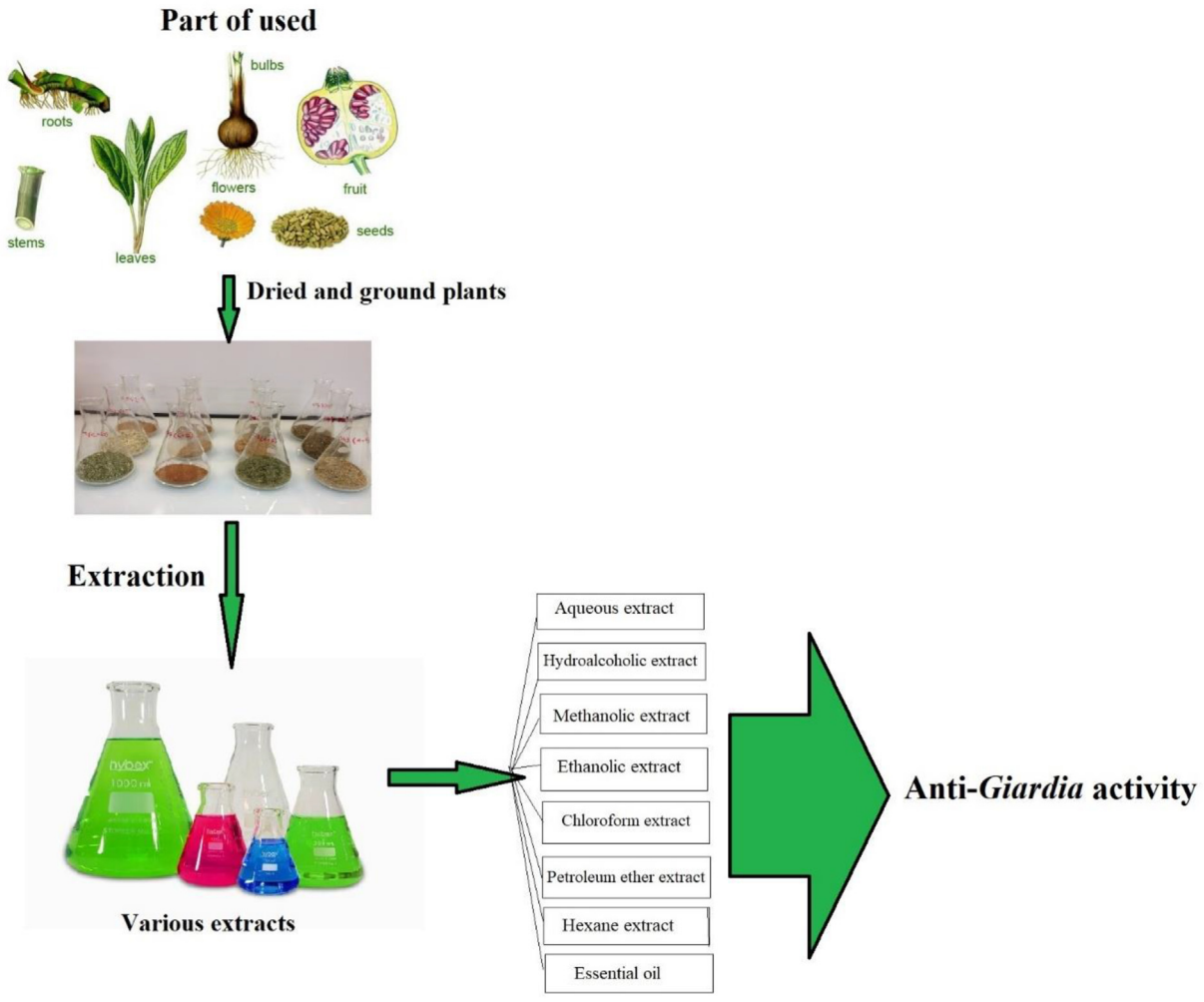

Fig. 2. Schematic representation of medicinal plants and their extracts of various parts used against *Giardia* infection.

present in herbs which make them a reliable source for preparation of new drugs (Pavarini et al., 2012; Ghasemzadeh et al., 2016).

Totally 48 plant species were demonstrated to be pharmacologically assessed for their anti-*Giardia* effects in the current review, whereas the most medicinal plants used belong to the family Lamiaceae followed by Asteraceae, Apiaceae. Studies have shown that plants from families Lamiaceae, Asteraceae, and Apiaceae due to high content phenolic compounds, flavonoids, terpenoids and exhibited a wide range of biological activities such as antimicrobial ones (Raja, 2012; Amiri and Joharchi, 2016; Bessada et al., 2015).

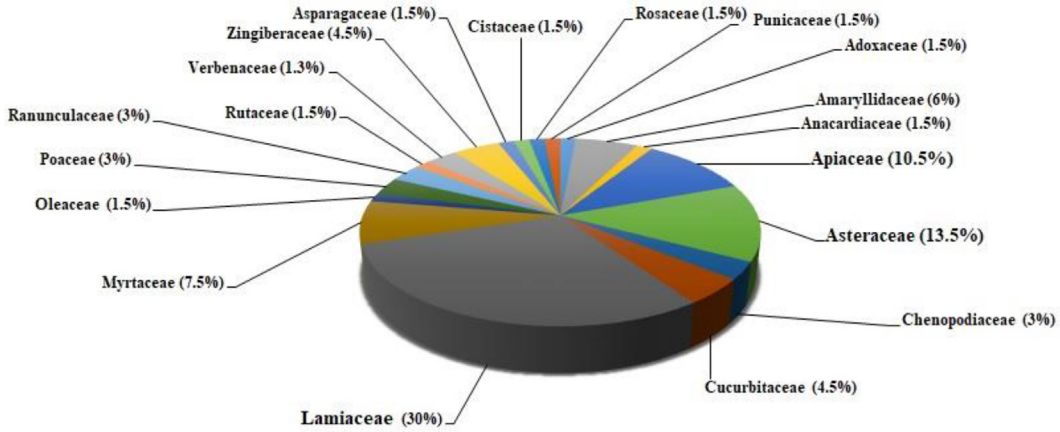

Fig. 3. Plant families evaluated for anti-*Giardia* activity. Totally 19 families were found the anti-*Giardia* activity *in vitro* and *in vivo*. The most widely used medicinal plants against *Giardia* infection belong to the family Lamiaceae (30.0%) followed by Asteraceae (13.f%), Apiaceae (10.5%).

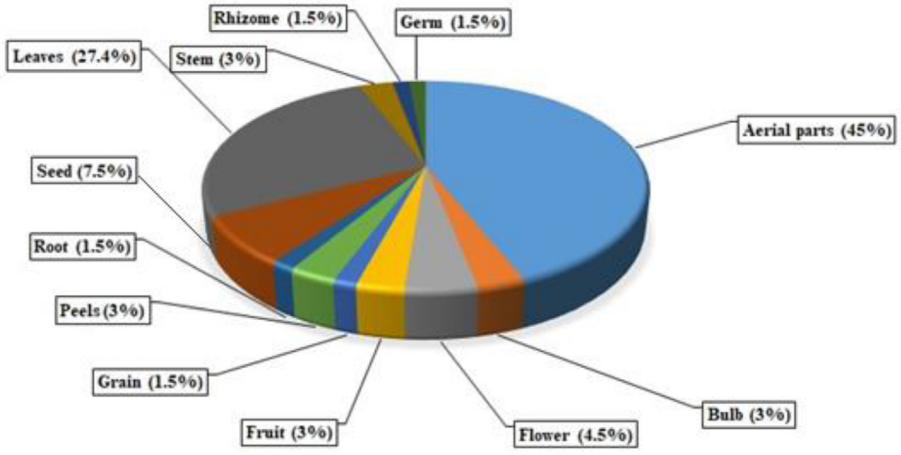

Fig. 4. The most parts of herbal medicines used for anti-*Giardia* activity. The obtained results showed that the most common parts used in the studies were aerial parts (45.0%) followed by leaves (27.4%) and seeds (7.5%). Whereas, other parts used were flowers, peels, bulb, and fruits.

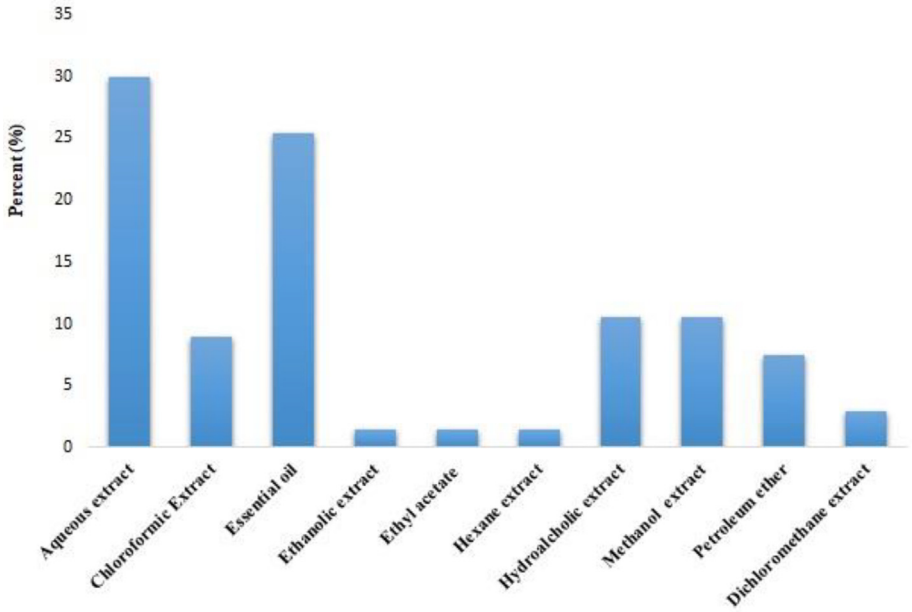

Fig. 5. The most type of formulations of herbal medicines used for anti-*Giardia* activity. The findings of the present review showed that aqueous extract (30.0%), essential oil (25.4%) and hydroalcholic and methanolic (10.5%) were considered as the desired approaches of herbal extraction, whereas the chloroformic (10.7%) and petroleum ether extract (7.5%) were the second most used herbal extractions.

Flavonoids as one of the main important secondary metabolites of herbs have various pharmacological and favorable health possessions such as antimicrobial activity (Tapas et al., 2008; Cushnie and Lamb, 2005). Based on previous studies, these compounds show their antimicrobial effects by membrane disruption, inhibit cytoplasmic membrane function, bacterial biofilm elimination, inhibition of cell envelope synthesis, inhibition of nucleic acid synthesis, inhibition of electron transport chain, ATP synthesis, inhibition of DNA gyrase, etc. (Xie et al., 2015; Górniak et al., 2019); therefore, the anti-*Giardia* activity of some plants could be related to the presence of the flavonoids compounds.

Another secondary metabolite of plants to which the antimicrobial effects of plants can be attributed is phenolic compounds (Trombetta et al., 2005). Reviews have demonstrated that polyphenols compounds show their antimicrobial effects through some mechanisms such as variation in permeability of cell membranes, the effect on some intracellular functions produced by hydrogen bonding of the phenolic components to enzymes, and change of the cell wall stability with entirety losses because of various interactions with the cell membrane (Daglia, 2012).

Terpenes (monoterpenes and sesquiterpenes) are one of the main plant-based compounds with a wide range of pharmacological and clinical properties such as antimicrobial ones (Mahizan et al., 2019). Studies showed that these compounds through microbial membrane disruption, interacting with intracellular organelles, and affecting critical cell activity have potent antimicrobial effects (Mahizan et al., 2019; Tariq et al., 2017); suggested that anti-*Giardia* effects of many plants are contributed to their high content of terpenoids.

Here, we found that aerial parts and leaves were the most frequently part of used during pharmacological confirmation of medicinal herbs against *Giardia* infection. Based on the previous investigations, leaves are considered as the preferred part of herbs by researchers for pharmacological goals because of having some properties such as (i) having a high amount of bioactive compounds; (ii) choose as a sustainable source of natural compounds; and (iii) ease of harvesting without damaging the plant (Eseyin et al., 2014; Moshi et al., 2012; Bhat et al., 2013; Altemimi et al., 2017).

The findings of our review showed that essential oil (28.6%) and aqueous extract (28.6%) were the most used herbal formulations. Previously it has been proven the general use of essential oil and aqueous extract highlight the role of solvents in extraction of potential bioactive constituents from various herbs and different parts of these plants (Al-Shaibani et al., 2008).

Based on the obtained results, we found that most of the investigations are aimed at *in vitro* model rather than *in vivo* assessment of herbs against the *Giardia* infection. This might be due to some unique features of this assay such as low cost, less time-consuming, and ease of doing and getting results, that let herbs screening on a large scale (Bedell et al., 1997). Although, *in vivo* assay would be more perfect and specific than *in vitro*, however it has some disadvantages such as higher cost, being time-consuming, and difficulty to repeat because the animal and pharmacodynamics in the host (Woo et al., 2012).

With all interpretations associated with the high efficiency of medicinal plants, but in recent years, there has been a rising concern about the toxicity and safety of medicinal plants (Bateman et al., 1998). Reviews have reported that adverse health effects of medicinal plants are attributed to some factors such as toxicity of main components, absence of adherence to proper manufacturing practice and subsequently contamination of preparations by means of heavy metals or microorganisms, and adverse reactions because of age, and genetic and underlying diseases of the user (Mensah et al., 2019).

5. Conclusion

In recent years, a wide range of researches are regularly studying on herbal extracts and essential oils to discover agents with potent anti-*Giardia* efficacy which could be applied for the giardiasis treatment alone or in combination with current synthetic drugs. The major advantages of herbal medicines over chemical medicines is that there are lower risks to develop resistance due to having a combination of different biological compounds with different mechanisms of action. The findings of the present review demonstrated that the plant-based anti-*Giardia* agents are up-and-coming as an alternative and complementary resource for treating giardiasis since had fewer significant toxicity. In addition to medicinal herbs, plant-derived compounds and compounds derived from natural products can be considered as promising products of effective to treatment of giardiasis. However, more studies are required to elucidate this conclusion, especially in clinical systems.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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