Secondary Metabolites as Potential Therapeutic Agents against Parasitic Infections

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Abstract

In the context of global health, parasitic diseases continue to be a significant challenge, particularly in developing countries with limited resources. The emergence of drug-resistant parasites and the undesirable side effects associated with conventional treatments have triggered the search for alternative therapeutic strategies. Secondary metabolites, which are natural compounds synthesized by organisms for ecological reasons, offer great promise as potential effective agents against parasitic infections. This book chapter aims to present a comprehensive summary of recent research on secondary metabolites with anti-parasitic properties, emphasizingtheir mechanisms of action, efficacy, and potential applications in the treatment of parasitic diseases.

Keywords- parasitic infections, metabolites, phytocompounds, Giardiasis, therapeutic agents.

Introduction

1. Secondary metabolites as therapeutic agents

Throughout their life cycle, plants create secondary metabolites (SMBs). These SMBs are produced from primary substances that act as their precursors, including as lipids, proteins, carbohydrates, and nucleic acids (Saltveit 2017). The range of organic compounds that fall under SMBs include terpenes, resins, alkaloids, flavonoids, and phenolic compounds, as depicted in Figure 1. These secondary metabolites contribute to the color, flavor, and fragrance of plants (Shitan 2016; Bansal et al., 2017; Symeonidou et al., 2018; Chanda and Ramchandra 2019). Notably, essential oils, polyphenols, and glycosidic glucosinolates extracted from various plant species, especially medicinal and aromatic plants, have demonstrated significant potential in combating diseases caused by various pathogens, owing to their remarkable antimicrobial activity.

2. Sources of Secondary Metabolites with Anti-Parasitic Activity

Numerous secondary metabolites have been sourced from plants, microorganisms, and fungi. For instance, alkaloids like morphine and quinine have been extracted from plants and employed as potent pain relievers and antimalarial medications, respectively. Additional examples encompass taxol, derived from the Pacific yew tree, utilized in treating different cancers, and artemisinin, obtained from *Artemisia annua*, known for its effectiveness against malaria. Secondary metabolites remain a valuable reservoir of new drug candidates, and their investigation offers great potential for the advancement of novel therapeutics to enhance human and animal well- being.

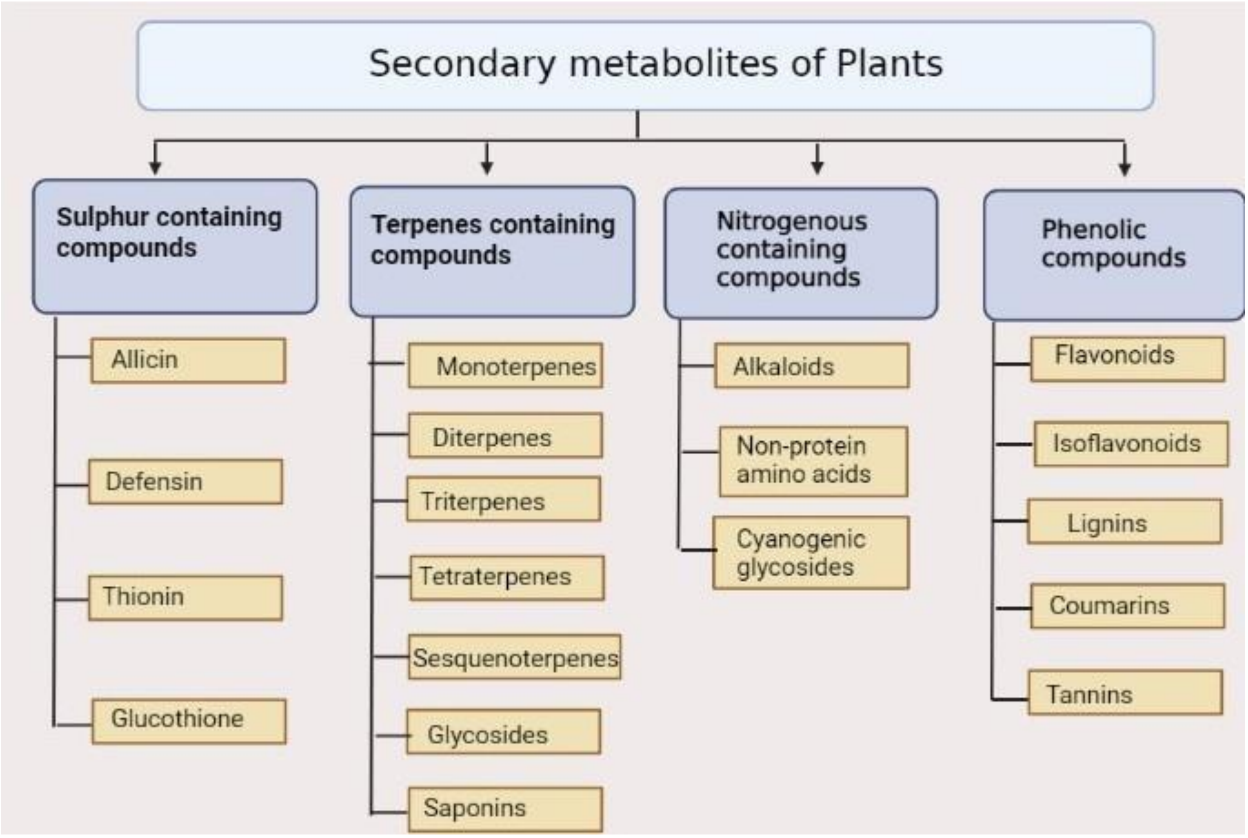

Figure 1: Classification of secondary metabolites of plants.

Several classes of secondary metabolites have demonstrated anti-parasitic potential. Alkaloids, terpenoids, flavonoids, quinones, and polyphenols are discussed in the following table **(Table 1)**.

1. Terpenes	Terpenes consist of distinct hydrocarbons formed by arranging various 5- carbon isoprene units. Within this category, glycosides and saponins are encompassed, their classification being determined by their respective structural characteristics.
2. Glycosides	Glycosides arise as substitutes for acetals, resulting from the interaction between monosaccharides and alcohol with the aid of an acidic catalyst.
3. Saponins	Saponins, often represented as SN, consist of either a triterpene or steroidal aglycone coupled with one or several chains of sugar. They are found in more than 100 plant families and act as active ingredients. Saponins are predominantly present in monocotyledons and less frequently in dicotyledons.
4. Phenolic compounds	Phenolic compounds: Phenolic compounds (PC) are characterized by a functional heterogeneous group with an aromatic ring. They are metabolites formed by the condensation of acetate units and include flavonoids, isoflavonoids, and tannins.

5. Flavonoids	Flavonoids (FN) are low molecular weight secondary metabolites that serve various functions such as defense mechanisms, safeguarding against UV radiation, inhibiting auxin transport, displaying allelopathic effects, and contributing to the pigmentation of flowers.
6. Tannins	Tannins (TN) are polyphenolic compounds soluble in water, with theability to cause proteins like gelatin to precipitate. These compounds are present in a wide range of plants, encompassing both trees and herbs.

Table 2. Mechanism of action of secondary metabolites against parasites.

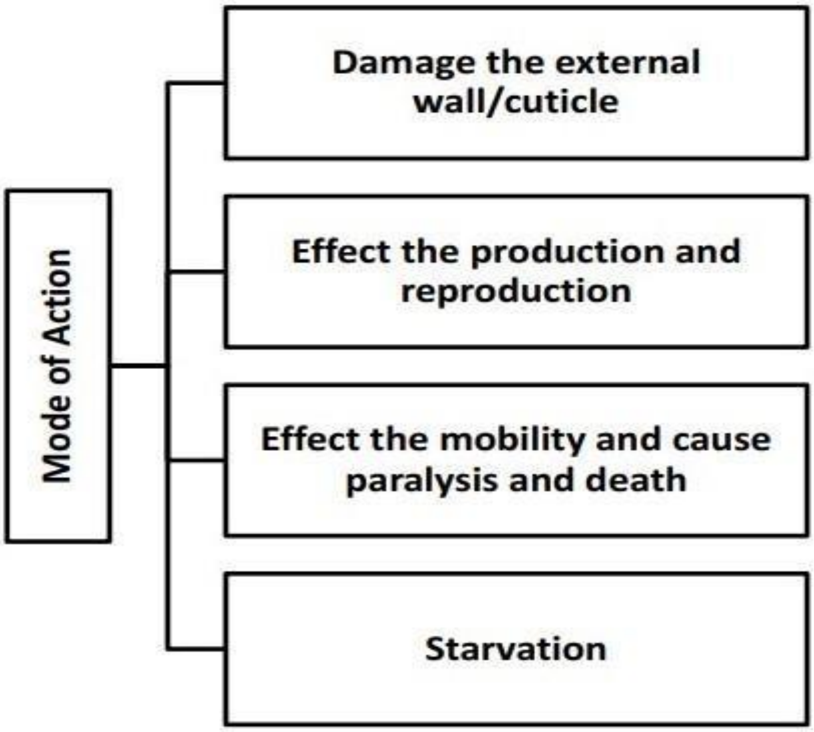

Table 3. Impact of parasitism on different hosts.

Class	Site of infection	Host	Parasites	Consequence of parasitism
Protozoa	Blood	Human	Plasmodium	Anemia
	Blood	Human Bovine White footed mouse	Babesia Ticks (Intermediatehost) *B. divergens* *B. mircoti* (Primary host: *Peromyscus leucopus;* secondary host: *Ixodes*)	Fever, chills, haemolytic anemia
Nematode	Abomasum	Sheep, goat	*Haemonchus contortus* *Teladorsagia circumcincta*	Anemia Reduced feed intake
	Small intestine	Sheep, goat	*Nematodirus battus* *Trichostrongylus colubriformis*	Reduced feed efficiency Reduced feed efficiency
	Abomasum	Cattle	*Haemonchus placei* *Ostertagia ostertagi*	Reduced feed intake Reduced feed intake
	Small intestine	Cattle	*Cooperia oncophora* *Cooperia punctata*	Reduced feed efficiency Reduced feed efficiency
Cestode	Small intestine	Human	*Taenia solium* *Taenia saginata*	Abdominal distress, anorexia, diarrhea, dyspepsia Nausea, appetite loss and weight loss
	Small intestine	Canids	*Echinococcus granulosa*	Pulmonary and liver cyst formation
	Small intestine	Rodents and human (intermediate host)	*Hymenolepis nana*	Headache, abdominal pain, diarrhoea

3. Secondary metabolites against protozoa

Protozoan diseases

Protozoan diseases pose significant economic and health challenges worldwide. These diseases, which affect both humans and livestock, include malaria, Trypanosomiasis, Chagas disease, leishmaniasis, and toxoplasmosis (Capela et al., 2019). The increasing prevalence of drug- resistant strains and the limited development of new drugs with innovative approaches have reduced the efficacy of current treatments for these diseases. Protozoa are microscopic, single- celled eukaryotic organisms found worldwide, with over 65,000 described species, many of which are free-living parasites. These organisms exhibit complex internal structures and intricatemetabolic activities (Shanan et al., 2015). The life cycle of protozoan parasites involves feeding trophozoites, which can be either intracellular or extracellular. Parasite transmission occurs through various modes, including the fecal-oral route, vector-borne transmission, and predatory- prey interactions (Imam et al., 2009; Antonovics et al., 2017). Additionally, protozoan parasites undergo a dormant stage, allowing them to survive in extreme conditions without oxygen and nutrients for extended periods.

Giardiasis

Giardia is a common flagellate of the intestine of mammals (Gardner and Hill, 2001). Giardia is a newly prominent parasite affecting livestock and diverse wildlife categories, spanning from birds to amphibians worldwide. Within the genus Giardia, numerous species share resemblances in terms of structure and possess multiple affiliations with different hosts. The infected animal may act as zoonotic potential of infection of *Giardia*. The transmission may occur from an infected animal to a healthy animal or human. However, the direct transmission of *Giardia* from infected animal to healthy animal or human still needs to be explored. The escalation of this ailment to a global health concern is attributed to the development of resistance to commonly employed drugs, compelling the exploration of plant-derived remedies for various parasitic infections. Pippali Rasayana, an Ayurvedic herbal remedy, is concocted from Piper longum (Pippali) and B. monosperma (Palash), utilizing the ash of the stem, root, flower, and leaves of B. monosperma. This preparation has displayed substantial efficacy against Giardiasis, exhibiting a recovery rate of up to 98% from infections (Agrawal et al., 1997). In vitro assessments have identified notable herbal contenders against G. lamblia, including Allium sativum, Artemisia sieberi, and Chenopodium botrys, demonstrating maximum impact at a concentration of 0.1% µg/ml. Helianthemum glomeratum methanolic extract exhibited exceptional effectiveness with an ED50 value of 0.125 mg/kg against giardiasis in animal models. Lavender's hydroalcoholic extract at a dose of 400 mg/ml exhibited potency against Giardia lamblia. Ferula assa-foetida's alcoholic extract displayed efficacy of 37% at 20 mg/ml concentration, reaching 100% by the 4th hour against Giardia lamblia. In Balb/C mice, Tanacetum parthenium's chloroform extract at 100 mg/ml concentration proved effective against Giardia lamblia. Another notable contender, the crude extract from Agereatum coniyzoides leaves, exhibited strong effectiveness against Giardia duodenalis trophozoites (Pintong et al., 2020). Furthermore, the potential of ethanolic extract from pomegranate peel was assessed against G. lamblia, revealing significant reduction in cysts and trophozoites within fecal matter and the intestines, respectively.

Toxoplasmosis

Toxoplasmosis, a zoonotic disease caused by the obligate parasite Toxoplasma, is widely distributed worldwide. *T. gondii*, a single species in the genus Toxoplasma belonging to the phylum Apicomplexa, can be life-threatening in individuals with weakened immune systems. In recent times, there has been increasing focus on exploring alternative treatments for parasitic diseases, leading to numerous studies in this area. Fungi have the capacity to produce a diverse array of secondary metabolites (Costa et al., 2016), including peptides, alkaloids, terpenes, polyketides, quinones, sterols, and coumarins. These secondary metabolites from fungi have shown effectiveness against protozoan infections.

Malaria

Plasmodium, a unicellular sporozoan protozoan parasite transmitted through the bite of infected Anopheles mosquitoes, causes malaria, which is more prevalent in tropical and sub-tropical regions worldwide. The four common species responsible for malaria are *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, with *P. falciparum* and *P. vivax* being the most common. In India, *Plasmodium vivax* is the primary cause of malarial infection (Anvikar et al., 2016). The World Health Organization (WHO) reports that the global malaria burden mainly originates from 15 countries in sub-Saharan Africa and the Indian subcontinent, with five of those countries, including India, accounting for half of all malaria cases (WHO, 2018).

Malaria treatment involves a range of available drugs like chloroquine, mefloquine, primaquine, and artemisinin. Yet, the rise of drug-resistant Plasmodium strains hampers their effectiveness significantly (Bahekar et al., 2013). Particularly, Plasmodium, notably P. falciparum causing tropical malaria, has demonstrated resistance to numerous synthetic medications. A remarkable stride in antimalarial drug development was the unveiling of artemisinin, a sesquiterpene lactone derived from Artemisia annua (Asteraceae). This compound has proven efficacy even against P. falciparum strains resistant to multiple drugs

(Willcox, 2011; Efferth et al., 2011). Currently, derivatives of artemisinin created through partial synthesis, such as the water-soluble artesunate, are being used in clinical applications (Kuhn and Wang, 2008). Medicinal plants often harbor intricate combinations of secondary metabolites, and there's a belief that these compounds work together synergistically when present in extracts (Wink, 2008). For instance, combining epigallocatechin 3-gallate (EGCG), a common polyphenol found in green tea, with the saponin digitonin has demonstrated synergistic effects in diminishing the mobility and viability of Plasmodium berghei (Hellmann et al., 2010).

Numerous plants have been identified as sources of anti-malarial medicinal properties, with the genus Artemisia being particularly notable. Essential oils and biomolecules derived from these plants, such as artemisinin from *Artemisia annua*, have shown antimalarial activity. Additionally, *Cinchona officinalis* and related species from the Rubiaceae family were among the first used for developing anti-malarial drugs, with quinoline alkaloids like quinine being effective against different developmental stages of the malaria parasite. Combinations of *Allium sativum* with other plants have also been suggested for the effective treatment of Plasmodium (Alebie et al., 2017).

Furthermore, various compounds derived from fungi, such as sterosterin A from *Stereum ostera*, Aurisin A, G, and K from *Neonothopanus nimbi* and *Anthracophyllum* species, Eurochevalierine from *Eurotium chevalieri*, and Hirsutellone F from Trichoderma spp. have exhibited anti- plasmodial effects, particularly against *P. falciparum*.

Coccidiosis

Coccidiosis, a major parasitic disease in poultry caused by protozoan parasites of the genus Eimeria, has a significant impact on the growth and feed utilization of infected birds, leading to productivity loss. This poultry disease affects the epithelial lining of the intestine and is prevalent worldwide. Infected birds may display symptoms such as droopiness, pale comb, diarrhoea, and occasional blood in droppings, with high mortality rates observed in both chicks and adults. Current strategies for preventing and treating coccidiosis include the use of anticoccidial chemicals, vaccines, and natural products. Plant-based phytochemicals have emerged as a promising and safe alternative for managing coccidiosis. Garlic and its sulfur compounds, such as allicin, alliin, ajoene, diallyl sulfide, dithiin, and allylcysteine, have been reported to exhibit broad antimicrobial activities, effectively inhibiting the sporulation of *E. tenella* in vitro (Alnassan et al., 2015; El-khatam et al., 2014; Pourali et al., 2014). Green tea extracts have also shown significant inhibition of coccidian oocyst sporulation, with selenium and polyphenolic compounds thought to be the active agents responsible for inactivating enzymes involved in sporulation. Studies on the extract of *Garcinia kola* demonstrated its anticoccidial activity against experimental *Eimeria tenella* infection in broiler chickens (Shetshak et al., 2020). *Azadirachta indica*, commonly known as neem, contains various compounds, including limonoids and protolimonoids, which are believed to influence Eimeria's life cycle (Biswas et al., 2002; Koul et al., 2006). In comparison to salinomycin sodium, neem fruit added to broiler diets showed efficient repression of coccidiosis (Tipu et al., 2002).

Furthermore, essential oils (EO) derived from aromatic plants and their constituents have displayed antimicrobial properties against bacteria and fungi in both laboratory experiments and living organisms (Rhayour et al., 2003, Chami et al., 2004, 2005, and Bennis et al., 2004). Recent research conducted by Remmal et al. (2011) demonstrated the efficacy of essential oils in destroying Eimeria oocysts in laboratory settings. The major components of EO, including carvacrol, carvone, isopulegol, thymol, and eugenol, were tested for their ability to eliminate Eimeria oocysts in a dose and time-dependent manner, as indicated by the release of substances absorbing at 273 nm.

Trichomoniasis

Trichomoniasis, caused by *Trichomonas vaginalis*, is a prevalent sexually-transmitted protozoan infection that primarily affects women but also affects men to a lesser extent. Globally, approximately 170 million people are infected, and this infection is often linked to HIV and cervical cancer (Gehrig et al., 2009). Due to the emergence of drug-resistant Trichomonas strains, there is a demand for new chemical treatments. Natural products, such as alkaloids like berberine, dibenzofurans, anthraquinones, polyacetylenes, saponins, and diterpenes, have been investigated as potential alternative therapies (Gehrig et al., 2009).

4. Secondary metabolites against nematodes

Lymphatic filariasis

Lymphatic filariasis (LF) poses a significant global health challenge, impacting approximately 120 million individuals in 72 countries. The disease is caused by nematode parasites *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, which are transmitted through mosquito bites from species like Culex, Anopheles, Aedes, and Mansonia (Lourens et al., 2019). LF is closely associated with lymphedema, commonly known as elephantiasis, resulting in swelling of limbs, breasts, and genitals. In response, the World Health Organization (WHO) has launched the Global Program to Eliminate Lymphatic Filariasis (GPELF) with the goal of curbing the spread of infection, eradicating LF, and alleviating the suffering of affected individuals. Current treatment strategies involve mass drug administration of drugs like Albendazole, Diethylcarbamazine (DEC), and Ivermectin, which target the microfilariae stages but are inadequate in eliminating adult worms. Consequently, research has explored the potential of herbal plants for their anti-filarial properties. Notably, *Oldenlandia herbacea*, *Buteamon sperma*, *Streblus asper*, and *Adansonia digitata* have exhibited significant anti-filarial effects both in laboratory studies and living organisms (Singh and Singh, 1987; Chatterjee et al., 1992; Ibrahim et al., 2014), and their use may aid in regulating inflammation associated with LF pathologies.

Ascaridiasis in poultry

Ascaridia galli, a parasitic nematode affecting poultry, presents a widespread and economically significant challenge on a global scale. Various anthelmintic agents, including piperazine, albendazole, levamisole, ivermectin, benzimidazole, and fenbendazole, have proven effective in managing A. galli infestations. Fenbendazole stands out due to its distinctive mode of action (Bazh and El-Bahy, 2013; Yazwinski et al., 2013; Umar et al., 2018). Certain plants contain secondary metabolites (SMBs) like terpenes (glycosides and saponins), phenolic compounds (flavonoids and tannins), and nitrogen-containing compounds (alkaloids, cyanogenic glycosides, and non-protein amino acids). These compounds exhibit anthelmintic properties by influencing nematodes through various mechanisms (Zaman et al., 2020). For instance, citrus peels housing Limonene, β-Pinene, α-Pinene, and Sabinene have displayed potential anthelmintic attributes against A. galli (Abdelqader et al., 2012).

Cysticercosis

Cysticercosis, a result of the pork tapeworm Taenia solium, has become a notable issue forpublic health and agriculture in underdeveloped areas across Latin America, Africa, and Asia. This concern arises particularly in regions where pigs are reared for consumption throughtraditional methods. This zoonotic ailment gives rise to cysts within both humans and pigs, ultimately causing epilepsy and fatalities in humans. Concurrently, it diminishes the market value of pigs and renders pork unfit for consumption. The transmission of T. solium occurs between humans and between humans and pigs, occasionally even exclusively among humans, resulting in the development of cysticercosis.

5. Secondary metabolites against trematodiasis

Schistosomiasis

Schistosomiasis is commonly managed through the administration of praziquantel, either as a standalone treatment or in conjunction with albendazole or ivermectin. Other therapeutic options encompass oxamniquine and antimalarial medications such as quinoline alkaloids and artemisinin, along with its derivatives. These treatments have been utilized for addressing the ailment (Mullner et al., 2011). Efforts against the vector snails, responsible for schistosomiasis transmission, namelyOncomelania, Biomphalaria, and Bulinus, have identified molluscicidal properties in various compounds. Anthraquinones present in Rheum palmatum and Rumex dentatus (Polygonaceae), phorbol esters derived from Jatropha curcas (Euphorbiaceae), and the broader category of saponins have displayed activity in this regard (Liu et al., 1997).

Furthermore, Curcumin and its derivatives, sourced from Curcuma plants (Zingiberaceae), have demonstrated parasiticidal effects against Schistosoma parasites (Haddad et al., 2011).

Table 4. Active phytocompounds for treatment of different parasitic diseases.

Family	PLANT NAME	ACTIVE COMPOUNDS	PARASITE TYPE	REFERENCE
Malvaceae	*Adansonia digitata*	Polysaccharide	Lymphatic filariasis	Ouedrago *et al.*, 2020
Fabaceae	*P. biglobosa*	Flavonoids, saponins, tanins and Triterpenes	Lymphatic filariasis	Saleh *et al.*, 2021
	Azadirachtis indica	Tetranotriterpenoids	Lymphatic filariasis	Mukherjee *et al.*, 2019

Lamiaceae	*Ocimum tenuiflorum*	Essential oil	Lymphatic filariasis	Malebo *et al.*, 2012
Lamiaceae	*Ocimum gratissimum*	Essential oil	Lymphatic filariasis	Malebo *et al.*, 2012
Lamiaceae	*Hyptis suaveolens*	Essential oil	Lymphatic filariasis	Malebo *et al.*, 2012

Family	**Plant**	**Active compound**	**Parasitic form**	**Concentration**	**Reference**
Laminaceae	*Lavandulastoechas L*	Flavonoids, phenolic acids, dipropenes, triplepenes, tannins, materials as bitter, resins, saponin	*G. lamblia*	400 mg/ml	Vazini *et al.*, 2017
Apicaceae	*Ferula assafoetida*	α-Pinene, β-pinene, sabinene, eremophilene, β-caryophyllene and himachalen-7-ol		20 mg/ml	Rezaee-Manesh and Shirbazou, 2012
Asteracecae	*Tanacetumparathenium*	Parthenolide		100 mg/ml	Elmi *et al.*, 2014
Asteraceace	*Allium paradoxum*	Limonen, Spathulenol, alpha-Bisabolol, Z-Nerolidol, n-Tricosane, n-Docosane		100 mg/ml	Elmi *et al.*, 2014
Apiaceae	*Carumcopticum*	Thymol, Trinin, Pinen and Myrcens		8 mg/ml	Shahabi *et al.*, 2008
Amaryllidaceae	*Allium ascalonicum*	Thymol and Carvacrol	Giardia	0.2 mg/ml	Azadbakht *et al.*, 2003
	Lippia berlandieri	Tannins and Vernalin		0.85 mg/ml	Ponce *et al.*, 1994

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