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Chemical Composition and Biological Significance of Thymol as Antiparasitic

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Abstract

Thymol is one of the most important phytochemical components because of its pharmacological and bioactive potential effects. This review focuses particularly on thymol as an alternative natural antiparasitic with potential use in the pharmaceutical industry. This is in line with the preferences of the natural products for treatment being safer and without side effects. The biosynthesis pathways of thymol and carvacrol have been discussed, and mechanism of action of thymol on parasites. Studies on thymol confirmed the activity of thymol as anti-parasite against anthelmintic, *Trypanosoma* ssp., *Toxoplasma gondii*, *Leishmania* spp., *Plasmodium falciparum*, *Giardia duodenalis*, *Eimeria* ssp., *Cryptosporidium baileyi* and *Cryptosporidium galli*.

Keywords

Thymol, Chemical Composition, Biological Activity, Antiparasitic

1. Introduction

A pathogen parasite is an organism that lives on the host organism causing harm and derives sustenance from its host, called medical parasitology. Parasitic disease is a type of infectious disease caused by parasites including parasitic protozoa, parasitic helminths (worms), and those arthropods that directly cause disease or act as vectors of various pathogens (ectoparasites). The diseases caused by these parasites constitute major human health problems throughout the

world, and sometimes the human infections caused by parasites can be fatal. Parasitic diseases also pose a threat to human life and health in developing countries in particular. Among the important tropical diseases are malaria, schistosomiasis, lymphatic filariasis, onchocerciasis, leishmaniasis, African trypanosomiasis, and chagas disease [1] [2] [3].

Currently, parasitic disease is still prevalent and a threat to human health. Therefore, infection with parasitic diseases is one of the challenges facing countries and scientists and the accurate diagnosis is of great importance and the first step to relieve the sufferings. The countries take great efforts to preserve human health by eliminating parasitic diseases such as schistosomiasis, malaria, filariasis, black fever, and ancylostomiasis in some countries, and many governments have achieved great success in controlling the prevalence of parasitic diseases jointly enacted by the United Nations Children's Fund, United Nations Development Program, World Bank and World Health Organization. Parasitic infections are occurring in all world areas, and the most parasitic infections are more prevalent in tropical countries [1] [2] [3].

However, treating diseases and eliminating the pathogen is still a dominant requirement throughout the ages in order to preserve the health of humans, animals, and plants. Thus, the discovery of new drugs is urgent that led to attention on the search for natural compounds as drugs due to the resistance of some parasites to the synthetic/chemical drugs [4]. For this, the use of phytotherapy has attracted interest from many scientists all over the world due to its biological activities variation related to the variability of their chemical composition, which is in turn influenced by genetic and environmental factors [5]. Note that the use of plants for treatment and other purposes dates back to the emergence of humanity, where it plays an important role in traditional medicine and drug development, including the use of essential oils extracted from medicinal plants [1] [6].

Essential oils are one of the principal fractions of chemical substances found in medicinal plants [7]. Terpenoids and phenylpropanoids are the main chemical compounds found in essential oil, that are widely used as bioactive molecules for many purposes such as biology, agronomy, medicine, and pharmaceutical sciences [8] [9] [10].

Among the prominent uses of essential oil, where it is included in the pharmaceutical industries and it has multiple medicinal uses as an anti-cancer, antitumor, antioxidant activity, antihelmintic, antivirus, antimicrobial, parasiticidal and also, insecticidal, larvicidal, and others as well as activity against diseases vectors [11]-[16]. Examples of some studies confirmed the activity of volatile oil as anti-parasite against intestinal parasites, such as *Blastocystis hominis*, *Entamoeba hartmanni*, *Endolimax nana*, *Eimeria tenella*, and *Pediculus humanus capitis* [17] [18] [19]. It is known that the biological activity of volatile oils is due to the synergism between their compounds or for the activity of each component separately [10]. Behnia *et al.* [20] concluded that, the antiamoebic effects of *Thymus vulgaris* essential oil against *Entamoeba histolytica*. Also, Hikal and Said-Al Ahl [14] showed that *Plectranthus amboinicus* essential oil has an-

ti-*Acanthamoeba* activity. These effects are attributable to the main components of the essential oils such as thymol [14] [21]. In this reference paper, we will investigate researches that dealt with the role of thymol its anti-parasite effects.

2. Plant Sources of Thymol

Herbs of the Labiatae family, are among the most common families that contain thymol in their essential oil and *Thymus vulgaris* is one of the most popular plants containing thymol. The quality of thyme essential oil is attributable to thymol. Apart from *Thymus vulgaris*, several important *Thymus* species have been reported for thymol sources. As shown in **Table 1**, medicinal herbs and their plant families and the percentage of thymol in the volatile oil produced by these plants.

3. Chemical Structure of Thymol

Thymol (2-Isopropyl-5-methylphenol) is a naturally occurring phenol monoterpene derivative of cymene and isomer of carvacrol (**Figure 1** and **Figure 2**).

There are many potential therapeutic uses of thymol for the treatment of disorders affecting the respiratory [54], nervous [55], and cardiovascular [56] systems, also thymol exhibits antimicrobial, antioxidant, anticarcinogenic, anti-inflammatory, and antispasmodic activities, as well as a potential as a growth enhancer and immunomodulator [57] as well as a potential as a growth enhancer and immunomodulator [58]. Moreover, the application of thymol for its antiparasitic properties has also been reported [57]. Besides, thymol was widely used to treat several helminth infections in man during [59].

In 2008, Wink [60], (Besides, thymol was widely used to treat several helminth infections in man during) has reported the mechanism of action of thymol indicating that thymol causes damage to cell function and structure due to its being highly lipophilic. Thymol may be easily absorbed by the cell membrane, thus causing destabilization of the phospholipid bilayer. It can alter the permeability of the outer and inner mitochondrial membranes of eukaryotic cells, leading to

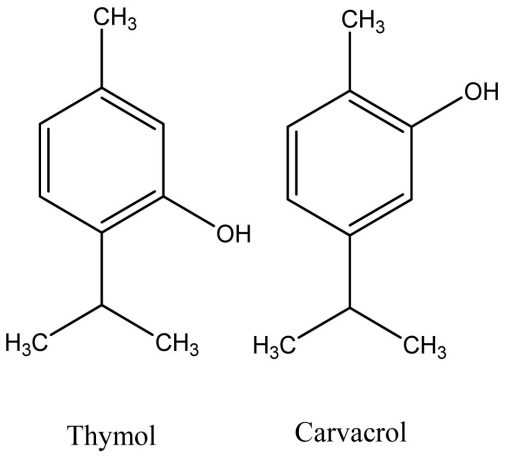

Figure 1. Structure of thymol and carvacrol.

Table 1. Some medicinal herbs containing thymol.

Family	Plant species	Reference
Lamiaceae	*Thymus vulgaris*	[22]
	Thymus musilii	[23]
	Thymus zygis; *Thymus hyemalis*; *Thymus glandulosus*	[24]
	Thymus lanceolatus	[25]
	Thymus daenensis	[26]
	Thymus capitatus	[27]
	Thymus satureioides subsp. pseudomastichina	[28]
	Thymus serpyllum	[29]
	Thymus spinulosu; *Thymus longicaulis* subsp. longicaulis	[30]
	Thymus ciliatus; *Thymus pallidus*	[31]
	Thymus broussonetii; *Thymus zygis*	[32]
	Thymus maroccanus; *Thymus satureoides*	[33]
	Monarda fistulosa; *Monarda didyma*	[34]
	Monarda punctata	[35]
	Monarda citriodora	[36]
	Monarda bradburiana	[37]
	Origanum vulgare	[38]
	Origanum syriacum	[39]
	Origanum compactum	[40]
	Plectranthus amboinicus	[41] [42]
	Marrubium vulgare	[43]
	Satureja montana	[44]
	Satureja spicigera; *Satureja intermedia*; *Satureja mutica*	[45]
	Satureja sahendica	[46]
	Zataria multiflora	[47]
Apiaceae	*Trachyspermum ammi*	[4]
	Oliveria decumbens	[5]
	Lagoecia cuminoides	[48]
Verbenaceae	*Lippia multiflora*	[49]
	Lippia gracilis	[50]
	Lippia sidoides	[51]
Asteraceae	*Baccharis grisebachii*; *Centipeda minima*	[52]
Scrophulariaceae	*Euphrasia rosstkoviana*	[53]

apoptotic effects. Likewise, thymol may inhibit enzymes involved in the protozoal metabolism, such as the ubiquitous enzyme dihydro folate reductase, which catalyzes the NADPH-dependent reduction of dihydrofolate to tetrahydrofolate,

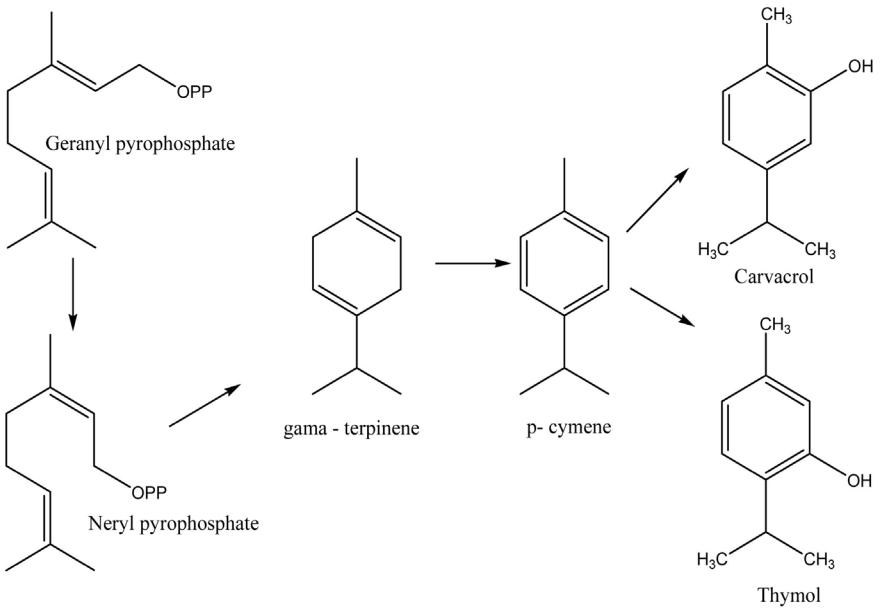

Figure 2. General biosynthesis pathways of aromatic monoterpenes thymol and carvacrol.

a precursor of cofactors required for the biosynthesis of purines, deoxythymidine triphosphate (dTTP), and several amino acids. Its inhibition results in a depletion of the folate pools, leading to the arrest of cell proliferation and cell death. In addition, they interact directly on the synthesis and activity of ATPase, and increase the overall permeability of the cytoplasmic membrane leading to induced cell death by processes associated with the loss of osmoregulation (e.g., leakage of ATP, potassium, and phosphate ions from the parasite).

4. Thymol Active against *Trypanosoma cruzi*

Trypanosoma cruzi parasite causes Chagas disease, also known as American trypanosomiasis, is a potentially life-threatening illness. An estimated 6 to 7 million people worldwide are infected with *T. cruzi* [61].

Trypanosoma cruzi infection is mostly transmitted when humans come into contact with feces and/or urine of infected blood-sucking triatomine bugs (vector-borne transmission). The parasites enter the body by skin break, the eyes or the mouth, or by consumption of food that has been contaminated with waste from infected triatomine bugs, causing outbreaks or oral transmission. Chagas disease can be also transmitted through blood or blood product transfusion from infected donors, during pregnancy or childbirth; and also organ transplantation from infected donors [61].

Symptoms are skin lesion or a purplish swelling of the lids of one eye (the so-called Romaña sign), fever, headache, enlarged lymph glands, pallor, muscle pain, difficulty in breathing, swelling, and abdominal or chest pain, cardiac disorders, experience digestive, neurological or mixed disorders. In later infection can lead to sudden death principally due to heart arrhythmia or heart failure

caused by the destruction of the heart muscle and its nervous system [61]. Benznidazole and nifurtimox are two treatments for chagas disease, but they should not be taken by pregnant women or by people with kidney or liver failure. Nifurtimox is also should not be taken for people with a background of neurological or psychiatric disorders [61].

Thymol compound, the major constituent of *Thymus vulgaris* essential oil has trypanocidal activity against *Trypanosoma cruzi*. Santoro *et al.* [62] showed effective thymol against epimastigotes and trypomastigote lysis of *Trypanosoma cruzi*, and added that thymol showed an IC_{50}/24h value of 62 μg/mL for epimastigotes and an IC_{50}/24h and value of 53 μg/mL for trypomastigotes. Moreover, thymol gave similar results to those obtained *in vitro* from treatment with the reference drug (benznidazole). Santoro *et al.* [62] explained that thymol permeates the cell membrane and kills the parasites by affecting cytoplasmic metabolic pathways or organelles, and not by compromising the parasite membrane integrity.

The result of another study on thymol as a major compound in the essential oil of *Lippia spp*., and *Thymus vulgaris* indicated that thymol had an effective against epimastigotes from *Trypanosoma cruzi* with IC_{50} values in the range of 5.5 to 32.2 μg/mL and thymol (IC_{50} 3.2 ± 0.4 μg/ml) was active against intracellular amastigotes of *T. cruzi*-infected Vero cells [63].

The same result was observed by Borges *et al.* [64], where that *Lippia sidoides* essential oil, which contains thymol (78.4%) as the main constituent has efficacy against disease epimastigote forms (IC_{50} values of 21.3, 26.2, and 28.9 μg/mL, respectively) from *Trypanosoma cruzi*. Juan *et al.* [65] confirmed that thymol exhibits anti-*Trypanosoma-cruzi* effect *in vivo*, when treating infected albino mice with thymol at a dose of mg/kg/day.

5. Thymol with Anti-*Trypanosoma brucei* Activity

Human African trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease. It is caused by infection with protozoan parasites belonging to the genus *Trypanosoma*. They are transmitted to humans by tsetse fly (*Glossina* genus) bites which have acquired their infection from human beings or from animals harbouring human pathogenic parasites, the disease is considered fatal without treatment [66].

Human African trypanosomiasis takes two forms: *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. *Trypanosoma bruceigambiense* form currently accounts for 98% of reported cases of sleeping sickness and causes a chronic infection. When more evident symptoms emerge, the patient is often already in an advanced disease stage where the central nervous system is affected. *Trypanosoma brucei rhodesiense* form represents under 2% of reported cases and causes an acute infection. Animals can host the human pathogen parasites, which domestic and wild animals are an important reservoir. Animals can also be infected with *Trypanosoma brucei gambiense* and probably act as a reservoir to a lesser extent [66].

There are more ways in which people are infected: bite of an infected tsetse fly, mother-to-child infection: the trypanosome can cross the placenta and infect the fetus, pricks with contaminated needles, through sexual contact. Symptoms appear in two stages; the first stage, the trypanosomes multiply in subcutaneous tissues, blood, and lymph. This is also called the haemo-lymphatic stage, which entails bouts of fever, headaches, enlarged lymph nodes, joint pains, and itching. In the second stage, the parasites cross the blood-brain barrier to infect the central nervous system. This is known as the neurological or meningo-encephalic stage. In general, this is when more obvious signs and symptoms of the disease appear: changes of behaviour, confusion, sensory disturbances, and poor coordination. Disturbance of the sleep cycle, which gives the disease its name, is an important feature. Without treatment, sleeping sickness is considered fatal although cases of healthy carriers have been reported [66]. The type of treatment depends on the form of the disease and the disease stage. Six different drugs are used for the treatment of sleeping sickness. Pentamidine is used for the treatment of the first stage of *T.b. gambiense* sleeping sickness and Suramin is used for the treatment of the first stage of *T.b. rhodesiense*. Melarsoprolis used for the treatment of the second stage of both gambiense and rhodesiense infections [66].

Costa *et al.* [67], have reported that thymol which is the constituent of both *Lippia graveolens* and *Origanum virens* essential oils showed high efficacy against *Trypanosoma brucei*. Also, Kpoviessi *et al.* [68], found that the volatile oil of *Ocimum gratissimum* extracted from the seeds, leaves and stem contains the thymol compound which was effective as anti-*Trypanosoma brucei* (IC_{50} of 27.23 ± 3.74 μg/mL). The same result was obtained by [69]. They announced that the treatment with thymol (IC_{50} of 22.86 μg/mL) showed efficacy against *Trypanosoma brucei*.

Tasdemir *et al.* [70], proved that thymol compound has trypanocidal (anti-trypanosomal) activity against *Trypanosoma brucei rhodesiense*, with IC_{50} values of 110 ng/mL. Although carvacrol is the main component (70.6%) and thymol (1.8%), in the volatile oil of *Origanum onites*. However, thymol gave a better result than carvacrol *in vitro* against *T. brucei* with IC_{50} values of 11.3 and 22.9 μg/mL [69]. Anti-*Trypanosoma cruzi* activity also was reported [62] [71]. Thymol exhibits high antioxidant activity, which could protect the protozoans and prevent the action of oxidative stress caused by the host's cellular immune response [72].

6. Thymol Active against *Toxoplasma*

Toxoplasmosis is caused by *Toxoplasma gondii*. *Toxoplasma gondii*, an intracellular coccidian protozoan parasite is endemic throughout most of the world. Risk is higher in developing and tropical countries, especially when people eat undercooked meat or shellfish, drink untreated water, or have extensive soil exposure. Congenital transmission can also occur if a woman is infected during pregnancy, also through ingestion of soil, or food contaminated with cat feces, and contaminated blood transfusion and organ transplantation [73].

Symptoms may include influenza-like symptoms or a mononucleosis syndrome with prolonged fever, lymphadenopathy, elevated liver enzymes, lymphocytosis, and weakness. Rarely, chorioretinitis or disseminated disease can occur in immunocompetent people. In severely immunocompromised people, severe and even fatal encephalitis, pneumonitis, and other systemic illnesses can occur. Infants with congenital toxoplasmosis are often asymptomatic, but eye disease, neurologic disease, or other systemic symptoms can occur, and learning disabilities, cognitive deficits, or visual impairments may develop later in life [73].

Treatment is reserved for acutely infected pregnant women and those with severe disease or who are immunocompromised. The recommended regimen includes pyrimethamine, sulfadiazine, and leucovorin (folinic acid). Alternative treatment regimens include clindamycin, atovaquone, and azithromycin [73].

The principal components of the *Satureja khuzestanica* essential oil are carvacrol, thymol, p-cymene, *β*-caryophyllene, linalool [74] [75]. Mahmoudvand *et al.* [76] showed that *Satureja khuzestanica* essential oil has anti-toxoplasmosis against *Toxoplasma gondii*. However, regarding the mechanism of action of phenolic compounds, such as carvacrol and thymol, it has been shown that these compounds are proton exchangers, thus dropping the gradient through the cytoplasmic wall. They cause the breakdown of proton-motrice force and reduction of the ATP pool, leading finally to cell death [77].

Thymol presents intriguing anti-*Toxoplasma* effects perhaps by acting on free radicals arising from tissue damage caused by the disease. *T. gondii* infections can cause devastating disease in immunosuppressed patients and through congenital infection of newborn babies [78]. They recommended the thymol as an anti-*Toxoplasma gondii in vivo* and highlight its safe use in animals.

7. Thymol Active against Leishmaniasis

The leishmaniases are a group of diseases caused by protozoan parasites from more than 20 *Leishmania* species. These parasites are transmitted to humans by the bite of an infected female phlebotomine sandfly. There are four main forms of the disease: cutaneous leishmaniasis, visceral leishmaniasis, also known as kala-azar, mucocutaneous leishmaniasis, and post-kala-azar dermal leishmaniasis. Cutaneous leishmaniasis is the most common form, visceral leishmaniasis is the most severe form and can be fatal if untreated, and mucocutaneous leishmaniasis is the most disabling form of the disease. Most people who become infected with the parasite do not develop any symptoms during their lifetime. Today, more than 1 billion people live in areas endemic for leishmaniasis and are at risk of infection. An estimated 30,000 new cases of visceral leishmaniasis and more than 1 million new cases of cutaneous leishmaniasis occur annually. Additionally, leishmaniasis can be classified as anthroponotic or zoonotic depending on whether the natural reservoir of the parasite is human or animal [79].

Cutaneous leishmaniasis usually produces ulcers on the exposed parts of the body, such as the face, arms, and legs. There may be many lesions, which can

cause serious disability. When the ulcers heal, they invariably leave permanent scars, especially for women and girls. Visceral leishmaniasis is characterized by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver and serious anaemia. If the disease is not treated, the fatality rate can be as high as 100% within 2 years. Mucocutaneous leishmaniasis produces lesions that can partially or totally destroy the mucous membranes of the nose, mouth and throat cavities and surrounding tissues. Post-kala-azar dermal leishmaniasis, a complication of visceral leishmaniasis, is characterized by a discoloured (hypopigmented) flat skin (macular) rash, combined with some slightly elevated (maculopapular) or elevated (nodular) rash, usually in patients who have recovered from visceral leishmaniasis. Post-kala-azar dermal leishmaniasis heals spontaneously in most cases in Africa but rarely in patients in India [79]. Regardless of the causative *Leishmania* species, antileishmanial treatment cannot provide a sterile cure, and the parasite remains in the human body and can cause a relapse when there is immunosuppression. Treatment is complex and should be administered by highly experienced health personnel. Most antileishmanial medicines are injectable [79].

Several studies indicated that thymol has anti-*Leishmania in vivo*, including Tisserand and Balacs's study [80] and his recognized the active effect of thymol against *Leishmania amazonensis* promastigote. Likewise, Silva *et al.* [81] confirmed from their study that thymol had antileishmanial agents against promastigote forms of *Leishmania amazonensis*.

Other studies carried out by [82] [83] showed that thymol had activity against promastigotes forms of *Leishmania chagasi* with IC_{50} values of 9.8 μg/mL. Also, Xavier *et al.* [84] demonstrated that thymol had activity against promastigotes forms of *Leishmania amazonensis*. In a recent study, Tasdemir *et al.* [70], reported that thymol had a higher leishmanicidal effect than carvacrol.

Robledo *et al.* [85] concluded the anti-*Leishmania panamensis* of thymol. Oliveira *et al.* [86] concluded that thymol extracted from *Lippia sidoides* has anti-*Leishmania chagasi*. However, De Medeiros *et al.* [87] showed that thymol extracted from *Lippia sidoides* essential oil has anti-*Leishmania amanuensis*. Similarly, Farias-Junior *et al.* [83] and Morales *et al.* [88], announced the same result that thymol has anti-*Leishmania chagasi* activity. Whereas De Morais *et al.* [89] found the leishmanicidal activity of thymol against both promastigotes and amastigotes of *Leishmania chagasi*.

Youssefi *et al.* [90] reported the leishmanicidal effects of thymol against *Leishmania chagasi* promastigotes (IC_{50} values 7.2 μg/mL). They added that thymol was the most effective and the safest metabolite with the lowest side effects on the hamster liver infected with *Leishmania chagasi* comparing with carvacrol and linalool. Overall, thymol and carvacrol are highly promising candidates for the development of effective and safe drugs in the fight against leishmanial. Besides, thymol at 10, 5, and 2.5 μg/mL was highly effective against *Leishmania infantum*. However, thymol and carvacrol, with IC_{50} (90) values of 7.2 μg/mL (16.4 μg/mL) and 9.8 μg/mL (18.2 μg/mL), respectively, showed

promising growth inhibition on *L. infantum* promastigotes [90].

In vivo, Jain and Jain [91] showed the anti-leishmanial activity of thymol led to a decrease in the number of liver amastigotes in histopathological samples in comparison with the control group. Furthermore, thymol had a stronger inhibitory effect on the *in vitro* and *in vivo* growth of *Leishmania infantum* compared to carvacrol. Moreover, the significance of thymol as anti-leishmanial activity alone or in combination with standard drugs (e.g., glucantime, amphotericin B) was promising and can also be used to improve efficacy in leishmaniasis treatment and to reduce the emergence of drug resistance and side effects.

Satureja bakhtiarica essential oil containing thymol had a potential effect against leishmaniasis higher than glucantime drug [92]. While glucantime inhibited only 27% of parasites at a concentration of 750 μg/mL, all promastigotes were killed in the presence of the essential oil at this concentration. Furthermore, the essential oil can kill the parasites even at a concentration of 150 μg/mL during the first incubation times (24 - 48 h), but this was not observed for glucantime. The higher effect of essential oil compared to glucantime as anti-*Leishmania* is attributable to the phenolic compounds thymol and p-cymene components in essential oil.

Moreover, Escobar *et al.* [63] found that thymol component found in *Lippia origanoides* essential oil had an IC_{50} of 4.4 μg/ml against *Leishmania chagasi* promastigotes and showed no toxicity in mammalian cells. Also, thymol isolated from *Lippia sidoides* essential oil showed anti-*Leishmania* action against promastigotes and amastigotes of *Leishmania amazonensis* [93] [94].

8. Thymol with Antimalarial Potential

Malaria is a major international public health problem. 91 countries reported an estimated 216 million infections and 445,000 deaths in 2016, according to the World Health Organization (WHO) World Malaria Report 2017. Malaria in humans is caused by protozoan parasites of the genus *Plasmodium*: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae*. In addition, *P. knowlesi*, a parasite of old world (Eastern Hemisphere) monkeys, has been documented as a cause of human infections and some deaths in Southeast Asia. *Plasmodium* species are transmitted by the bite of an infective female *Anopheles mosquito*. Occasionally, transmission occurs by blood transfusion, organ transplantation, needle sharing, nosocomially, or from mother to fetus [95].

Malaria is characterized by fever and influenza-like symptoms, including chills, headache, myalgias, and malaise; these symptoms can occur intermittently. In severe disease, seizures, mental confusion, kidney failure, acute respiratory distress syndrome, coma, and death may occur. Suspected or confirmed malaria, especially *P. falciparum*, is a medical emergency requiring urgent intervention, as clinical deterioration can occur rapidly and unpredictably [95].

Malaria can be treated effectively early in the course of the disease, but a delay of therapy can have serious or even fatal consequences. Specific treatment options depend on the species of malaria, the severity of infection, the likelihood of

drug resistance (based on where the infection was acquired), and the patient's age and pregnancy status [95].

Tasdemir *et al.* [70] showed that thymol has antimalarial potential-plasmocidal (*P. falciparum*) potentials. Also, proved that carvacrol (70.6%), is the main component of the *Origanum onites* essential oil whereas thymol, which exists therein with much lower abundance (1.8%), exhibited *in vitro* antimalarial potential-plasmocidalequal to carvacrol.

Previous studies carried out by Mota *et al.* [96] confirmed the effectiveness of thymol as an anti-malaria *in vitro* with IC_{50} value of 4.5 μg/mL. Also, Fujisaki *et al.* [97] concluded that thymol component in oregano essential oil showed *in vitro* antimalarial activity against *P. falciparium* with an IC_{50} value of 10 μg/mL. Moreover, the activity of thymol is attributed to the characteristic feature of the phenolic hydroxyl group, which may be more acidic than carvacrol, and hence more active, due to the presence of a system of delocalized electrons [98] [99].

Satureja thymbra essential oil is rich in thymol, showed high *in vitro* anti-plasmodial activity against *Plasmodium falciparum* [100], causing enzyme (plasmepsins) inhibition at a concentration very close to that needed for killing the parasite. Also, Mota *et al.* [96] mentioned that, thymol, the main component of *Lippia sidoides* essential oil exhibited antimalarial activity against *Plasmodium berghei* in mice and *Plasmodium falciparum in vitro*.

Origanum compactum essential oil rich in thymol showed anti-plasmodial activity *in vitro* [101]. While, *Thymus vulgaris*, *Thymus serpyllus*, and *Myrtus communis* essential oils rich in thymol showed to be repellent against *Aedes*, *Anopheles* and *Culex* mosquitoes [102] [103]. However, thyme essential oil is patented for anophelifuge activity [104]. Several previous studies have demonstrated the anti-malarial efficacy of the volatile oils of *Thymus transpicatus*, *Thymus vulgaris* and *Myrtus communis* rich in thymol as larvicidal activity against *Anopheles* [100] [105] [106] [107].

9. Thymol against Giardiasis

The anaerobic protozoan parasite *Giardia duodenalis* (formerly known as *G. lamblia* or *G. intestinalis*) is endemic worldwide. *Giardia* is transmitted via the fecal-oral route. Its low infectious dose, protracted communicability, and moderate chlorine tolerance make *Giardia* ideally suited for transmission through drinking and recreational water. Transmission also occurs through contact with feces (for example, when providing direct patient care or during sexual activity), eating contaminated food, or contact with fecally contaminated surfaces [108].

Many infected people are asymptomatic, though if symptoms develop, they typically develop 1 - 2 weeks after exposure and generally resolve within 2 - 4 weeks. Symptoms include diarrhea (often with foul-smelling, greasy stools), abdominal cramps, bloating, flatulence, fatigue, anorexia, and nausea. Sometimes upper gastrointestinal symptoms are prominent. Weight loss may occur over time. Fever and vomiting are uncommon. Reactive arthritis, irritable bowel syn-

drome, and other chronic symptoms sometimes occur after infection with *Giardia*. Effective treatments include metronidazole, tinidazole, and nitazoxanide [108].

Machado *et al.* [109] observed that carvacrol, thymol, and eugenol had antigiardial activity against *Giardia lamblia* trophozoite. Also, *Thymbra capitata*, *Origanum virens*, *Thymus zygis* subsp. Sylvestris and *Lippia graveolens* essential oils rich in thymol inhibited the growth of *Giardia lamblia*. Moreover, *Lippia graveolens* had great potential as treatment agents for giardiasis caused by *Giardia lamblia* and *Thymus capitata* oil was the most active [110].

10. Thymol against Cryptosporidiosis

Among the many protozoan parasites in the genus *Cryptosporidium*, *Cryptosporidium hominis* and *C. parvum* cause > 90% of human infections. Cryptosporidiosis is endemic worldwide, and the highest rates are found in developing countries [111].

Cryptosporidium is transmitted via the fecal-oral route. Its low infectious dose, prolonged survival in moist environments, protracted communicability, and extreme chlorine tolerance make *Cryptosporidium* ideally suited for transmission through contaminated drinking or recreational water (such as the swimming pool). Transmission can also occur through eating contaminated food, through contact with infected animals (particularly preweaned bovine calves) or people (for example, when providing direct care or during oral-anal sex), or through contact with fecally contaminated surfaces [111].

Symptoms (most commonly, profuse, watery diarrhea) begin within 2 weeks (typically 5 - 7 days) after infection and are generally self-limited. Other symptoms can include abdominal pain, flatulence, urgency, nausea, vomiting, and low-grade fever. In immunocompetent people, symptoms typically resolve within 2 - 3 weeks; patients may experience a recurrence of symptoms after a brief period of recovery and before complete symptom resolution. Extraintestinal cryptosporidiosis (in the biliary or respiratory tract and rarely the pancreas) has been documented in children and immunocompromised hosts [111].

Tanghort *et al.* [112] recommended Thymol for fighting cryptosporidiosis (*Cryptosporidium baileyi* and *Cryptosporidium galli*) due to its destructive effect on oocysts at very low concentrations. There are well-known drugs against parasites such as albendazole. Currently, the only FDA drug approved for Crypto is nitazoxanide, but there are limitations and recommended thymol as anticreptospiridium [113].

11. Thymol against Anthelmintic

A large part of the world's population is infected with 1 or more of these helminths, and the prevalence is highest in tropical and subtropical countries where water supplies and sanitation are poor. *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* (hookworm), *Necator americanus* (hookworm), and *Tri-*

churis trichiura (whipworm) are helminths (parasitic worms) that infect the intestine and are transmitted via contaminated soil. Eggs are passed in feces from an infected person. Hookworm eggs are not infective-the eggs must hatch and release larvae that need to mature in the soil before they become infective. Infection with roundworm and whipworm occurs when eggs in soil have become infective and are ingested. Hookworm infection usually occurs when larvae penetrate the skin of people walking barefoot on contaminated soil. However, the hookworm *Ancylostoma duodenale* can also be transmitted when larvae are ingested [114].

Most infections are asymptomatic, especially when few worms are present. Pulmonary symptoms (Löffler syndrome) occur in a small percentage of patients when roundworm larvae pass through the lungs. Löffler syndrome is associated with fever and marked eosinophilia. Roundworms can also cause intestinal discomfort, obstruction, and impaired nutritional status. Hookworm infection can lead to anemia due to blood loss and chronic protein deficiency. Whipworm infection can cause chronic abdominal pain, diarrhea, blood loss, dysentery, and rectal prolapse. The most commonly used drugs for treatment are albendazole and mebendazole [114].

11.1. Thymol against *Ascaris*

Ascaris lumbricoides is the most prevalent soil-transmitted helminth infection of human beings worldwide. Chemotherapy with synthetic anthelmintics such as albendazole, mebendazole, and pyrantel pamoate is the current method of treatment; however, the emergence of anthelmintic resistance could substantially decrease the efficacy of such treatments. Additionally, benzimidazoles are not recommended for pregnant women or children under age one [115]. Hence, Kaplan *et al.* [115] conducted a study on the effect and efficacy of two microencapsulated, plant-based essential oil blends such as α-pinene, linalyl acetate, p-cymene, and thymol octanoate on helminths. The study concluded that α-pinene, linalyl acetate, p-cymene, and thymol octanoate promise as a daily supplement to reduce infection burdens of soil-transmitted helminths in both pigs and human beings.

11.2. Thymol against *Echinococcus* Tapeworms

Echinococcosis is a parasitic disease caused by infection with tiny tapeworms of the genus *Echinococcus*. Echinococcosis is classified as either cystic echinococcosis or alveolar echinococcosis [116].

Cystic echinococcosis, also known as hydatid disease, is caused by infection with the larval stage of *Echinococcus granulosus*, found in dogs (definitive host) and sheep, cattle, goats, and pigs (intermediate hosts). Although most infections in humans are asymptomatic, cystic echinococcosis causes harmful, slowly enlarging cysts in the liver, lungs, and other organs that often grow unnoticed and neglected for years [116].

Cystic echinococcosis is caused by infection with the larval stage of *Echinococcus granulosus*. It is found in Africa, Europe, Asia, the Middle East, Central and South America, and in rare cases, North America. The parasite is transmitted to dogs when they ingest the organs of other animals that contain hydatid cysts. The cysts develop into adult tapeworms in the dog. Infected dogs shed tapeworm eggs in their feces which contaminate the ground. Sheep, cattle, goats, and pigs ingest tapeworm eggs in the contaminated ground; once ingested, the eggs hatch and develop into cysts in the internal organs. The most common mode of transmission to humans is by the accidental consumption of soil, water, or food that has been contaminated by the fecal matter of an infected dog. Echinococcus eggs that have been deposited in the soil can stay viable for up to a year. The disease is most commonly found in people involved in raising sheep, as a result of the sheep's role as an intermediate host of the parasite and the presence of working dogs that are allowed to eat the offal of infected sheep [116].

Alveolar echinococcosis disease is caused by infection with the larval stage of *Echinococcus multilocularis*, found in foxes, coyotes, and dogs (definitive hosts). Small rodents are intermediate hosts for *E. multilocularis*. Although cases of alveolar echinococcosis in animals in endemic areas are relatively common, human cases are rare. Alveolar echinococcosis poses a much greater health threat to people than cystic echinococcosis, causing parasitic tumors that can form in the liver, lungs, brain, and other organs. If left untreated, alveolar echinococcosis can be fatal [116]. Infection with the larval stages is transmitted to people through the ingestion of food or water contaminated with tapeworm eggs [116].

In the past, surgery was the only treatment for cystic echinococcal cysts. Chemotherapy, cyst puncture, and percutaneous aspiration, injection of chemicals and respiration have been used to replace surgery as effective treatments for cystic echinococcosis. However, surgery remains the most effective treatment to remove the cyst and can lead to a complete cure. Some cysts are not causing any symptoms and are inactive; those cysts often go away without any treatment. The treatment of alveolar echinococcosis is more difficult than cystic echinococcosis and usually requires radical surgery, long-term chemotherapy, or both [116].

Albani *et al.* [117] state that, human alveolar echinococcosis is caused by the fox tapeworm *Echinococcus multilocularis* and is usually lethal if left untreated. The current strategy for treating human alveolar echinococcosis is surgical resection of the parasite mass complemented by chemotherapy with benzimidazole compounds. They added that combined benzimidazole with thymol treatment exhibited higher treatment efficiency compared with the drugs applied separately against murine experimental alveolar echinococcosis. In such a way thymol would be a useful option for the treatment of human alveolar echinococcosis.

Elissondo *et al.* [118] concluded that thymol has a clear effect of thymol against *Echinococcus granulosus* protoscoleces *in vitro*. Moazeni *et al.* [119] found that essential oil of *Trachyspermum ammi* rich in thymol (50.07%),

γ-terpinene (23.92%) and p-cymene (22.9%) has effect against *Echinococcus* tapeworms protoscoleces. They concluded that scolicidal power of *Trachyspermum ammi* essential oil at a concentration of 3 mg/mL was 31.34%, 35.98%, 45.17%, and 51.58% after 10, 20, 30, and 60 min, respectively. Besides, one hundred percent scolicidal activity was observed with *Trachyspermum ammi* essential oil at concentration of 10 mg/mL after 10 min of exposure. The results of this study revealed that the essential oil of *Trachyspermum ammi* is rich in thymol, *γ*-terpinene and p-cymene, has high scolicidal power and may be used as a natural scolicidal agent.

Elissondo *et al.* [118] [120] concluded that thymol was affected againstprotoscoleces, microcysts, and cysts of *Echinococcus granulosus in vitro*. Also *Trachyspermum ammi* essential oil contains thymol confirmed against protoscoleces of *Echinococcus granulosus* [119] [121] [122] [123]. In a study on essential oils of *Thymus vulgaris* rich in thymol and *Origanum vulgare* rich in thymol and carvacrol on anthelmintic effect, Pensel *et al.* [124] found an effective effect against protoscoleces and cysts of *Echinococcus granulosus*. The results showed that thymol had a considerably greater effect than carvacrol. Thymol and essential oils of *Thymus vulgaris* and *Origanum vulgare* can induce apoptosis in the cells of protoscoleces [124] [125].

11.3. Thymol against *Haemonchus contortus*

Haemonchus contortus is one of the principal stomach worms of sheep, and infection is characterized by anemia. Gastrointestinal nematode infections have an important negative impact on small ruminant production. *Haemonchus contortus* is the most economically significant parasite of sheep and goats throughout much of the United States and the world, due to the severity of the parasitism and the emerging anthelmintic resistance. Haemonchosis also affects New World camelids. It is a common cause of death in all these species [126] [127] [128] [129].

The most common clinical signs are failure to thrive and weight loss. As worm burdens increase, more severe signs, such as anemia, hypoproteinemia, submandibular edema (bottle jaw), weakness, and collapse, may develop. Unlike other gastrointestinal nematodes, *Haemonchus contortus* does not usually cause diarrhea. Due to the nonspecific signs and lack of diarrhea, haemonchosis is often undiagnosed until death. The death can appear suddenly, even though the course of infection may have been prolonged [126] [127] [130].

A major problem facing the sheep industry is resistance to macrolide dewormers, such as ivermectin and moxidectin. *Haemonchus contortus* has also been resistant to benzimidazoles (e.g., fenbendazole), tetrahydropyrimidines (e.g., pyrantel), and levamisole [126] [127].

Haemonchus contortus is an important gastrointestinal parasite on sheep farms in tropical regions and due to the resistance of *Haemonchus contortus* against most anthelmintic drugs represents a great economic problem to sheep

farming and is a major challenge that needs to be overcome. Ferreira *et al.* [131] found that thymol, the main component in *Thymus vulgaris* essential oil is the most important compound responsible for the anthelmintic. The *in vitro* results validated the popular use of *T. vulgaris* oil as an anthelmintic agent against *H. contortus*. Both the essential oil and thymol (50.22%) were effective against the three main stages of *H. contortus*. The essential oil and thymol were able to inhibit egg hatching by 96.4% - 100%, larval development by 90.8% - 100%, and larval motility by 97% - 100%. The essential oil and thymol completely inhibited the motility of *H. contortus* adults within the first 8 h of the experiment.

From André and co-workers [132] experience on the effect of thymol and thymol acetate on *Haemonchus contortus*, they found that thymol (0.5 mg/mL) and thymol acetate (4 mg/mL) inhibited larval hatching by 98% and 67.1%, respectively. Thymol and thymol acetate (8 mg/mL) inhibited 100% of larval development. Thymol and thymol acetate (800 µg/mL) reduced the motility of adult worms, by 100% and 83.4%, respectively. Thymol caused cuticular changes in adult worm teguments. In the acute toxicity test, the LD_{50} of thymol and thymol acetate were 1350.9 mg/kg and 4144.4 mg/kg, respectively. Thymol and thymol acetate reduced sheep egg count per gram of faeces (epg) by 59.8% and 76.2%, respectively. *In vitro* tests, thymol presented better anthelmintic activity than thymol acetate. However, thymol acetate was less toxic and in *in vivo* test efficacy was similar.

12. Thymol against Coccidiosis

Coccidiosis is a disease caused by parasites of the genus *Eimeria* and *Isospora* belonging to the phylum Apicomplexa with a complex life cycle, affecting mainly the intestinal tract of many species of mammals and birds, especially chickens. The economic significance of coccidiosis is attributed to decreased animal production (higher feed conversion, growth depression and, increased mortality) and the costs involved in treatment and prevention. Worldwide, the annual costs inflicted by coccidiosis to commercial poultry have been estimated at billions of Euro, stressing the urgent need for more efficient strategies to control this parasite [133].

Symptoms of coccidiosis in chickens (high mortality rates, characteristic intestinal lesions, watery/bloody faeces, etc.). Mortality, morbidity, diarrhoea or bloody faeces, and sub-clinical coccidiosis manifest mainly by poor weight gain and reduced efficiency of feed conversion and gives rise to the highest proportion of the total economic losses [134].

Numerous anticoccidial drugs such as sulphaquinoxaline and nitrofurazone were first approved by the American Food and Drug Administration. Most of the anticoccidial products currently approved in different regions of the world for the prevention of coccidiosis in chickens are amprolium, ethopabate, aprinocid, clopidol, decoquinate, diclazuril, dinitolmide (zoalene), halofuginone, nequinate (methyl benzoate), nicarbazin, robenidine, lasalocid, maduramicin, mo-

nensin, narasin, narasin + nicarbazin, salinomycin and semduramycin [133]. Teichmann's study and coworkers [135] on parasite *Eimeria* in the laboratory showed the effectiveness of thymol in relieving the symptoms of the coccidiosis disease when thymol was added to the diet or added with to anticoccidial drug lasalocid.

13. Conclusion

Thymol is naturally phytochemical found in a lot of medicinal herbs and widely used in many potential therapeutic uses, to treat several parasite infections. Numerous studies conducted on thymol have confirmed its effectiveness as an anti-parasite. Further research on thymol activities is still needed for details and information about the mechanism of action of thymol against parasites and each species separately. In this review, an update of the potential of thymol is active against some neglected diseases. The compiling of this review is intended to know the pathogen that caused parasitic disease and thus to provide the basis for treating the diseases by phytotherapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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