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REVIEW ARTICLE PUJ

Herbal Medicine and Parasitic Diseases

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INTRODUCTION

Herbal medicine (also known as traditional, folk and alternative medicine) comprises medical knowledge systems that developed over generations within various societies before the era of modern medicine. WHO defines traditional medicine as the health practices, approaches, knowledge and beliefs incorporating plant, spiritual therapies and manual techniques, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being[1]. Ancient Egyptian medicine, 1000 Before Christ (BC), was known to use garlic, opium, castor oil, coriander, mint and other herbs for medicinal purposes and Indian medicine used turmeric (Curcumin) possibly as early as 1900 BC[2]. *N. sativa* seeds have been used as a traditional medicine for the treatment of a variety of sicknesses including parasitic diseases[3]. The scope of herbal medicine sometimes extended to include fungal and bee products, as well as minerals, shells and certain animal parts[4]. It is estimated that 20,000 species of higher plants are used medicinally throughout the world. In some Asian and African countries, up to 80% of the population rely on traditional medicine for their primary health care needs[1].

The emergence of parasites resistant to current chemotherapies highlights the importance of plant essential oils as novel anti-parasitic agents; e.g., in schistosomiasis[5], malaria[6] and visceral leishmaniasis[7]. Some plant oils have immunomodulatory effects that could modify host-parasite immunobiology and the lipid solubility of plant oils might offer alternative, transcutaneous delivery routes[8]. In addition, the safety and use of plant essential oils in drug resistant cases are considered the most advantages. However, lack of proper understanding of plant and drug interactions have led to adverse reactions that are sometimes life threatening or lethal[9]. Furthermore, adulteration or counterfeit herbs can also be a health hazard; as WHO confirmed that inappropriate use of traditional medicines or practices can have negative or dangerous effects[1].

The present review is an analysis to through light on different herbs with their active compunds that could be used as drug targets in parasitic diseases. It also discusses some herbs with repellent activity and molluscicidal effects.

Keywords: Herbal Medicine, Parasitic Diseases, Treatment, Repellents, Molluscicides.

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Examples of Known Herbs with Antiparasitic Effects

***Allium cepa*; Onion (Al-Basal)**

Two sets of compounds make up the majority of onion's known active constituents: Sulphur compounds such as allicin and allyl propyl disulphide and flavonoids such as quercetin. Allicin exhibits its antimicrobial action mainly by immediate and total inhibition of RNA, DNA and protein synthesis[10].

In a study conducted in 2004, all tested strains of *Leishmania* (*major, donovani* and *mexicana*) were found to be sensitive *in vitro* to the onion juice in the promastigote stage[11]. Aqueous onion extract is similar to metronidazole in inhibiting both multiplication and motility of *T. vaginalis*[12]. *A. cepa* oil has an antihelminthic effect in rats experimentally infected with *T. spiralis* and increases the production of antibodies generated during life cycle of the parasite[13]. Recently, effectiveness of *A. Cepa* extract in eyelids inflammation caused by *Demodex folliculorum* was tested with promising results[14]. Onion reportedly exerted different physiological changes in snails of *B. alexandrina* leading to decrease in glucose and glycogen which are the snail energy fuel and inhibited the phenol oxidase enzyme which led to disturbance in egg-shell formation[15]. Some adverse effects have been reported where higher intakes may worsen existing heartburn and there are also isolated reports of allergy manifesting as skin rash and red, itchy eyes[16].

Allium sativum; **Garlic (Al-Tom)**

The active constituents of garlic exceed 200 chemicals. It contains sulphur compounds (allicin, alliin and agoene), volatile oils, enzymes (allinase, peroxidase and miracynase), carbohydrates (sucrose and glucose), minerals (selenium), amino acids such as cysteine, glutamine, isoleucine and methionine, bioflavonoids such as quercetin and cyanidin, Allistatin I and Allistatin II and vitamins A, B1, B2, C, E and niacin[17]. The main antimicrobial effect of allicin is due to its chemical reaction with thiol groups of various enzymes e.g. alcohol dehydrogenase and DNA polymerase which affect the essential metabolism of cysteine proteinase activity involved in the virulence of parasites[18]. Garlic appears to be safe during pregnancy and breast-feeding. Some sensitive people may experience heartburn and flatulence[19].

Antiprotozoal effects: Several studies were conducted to investigate the efficacy of garlic in giardiasis. There were reports of complete relief of clinical symptoms within 36 hours[20], loss of flagellar movement and motility with trophozoites swelling leading to decreased ability to adhere to host cells[21], inhibition of *Giardia*'s cysteine proteases activity and excretory/secretory products resulting in reduction of GIT symptoms[22]. The therapeutic effect of allicin was evaluated against *C. cayetanensis* and the results showed that Tomex (10 mg/Kg/day of garlic extract) caused significant reduction in oocyst shedding and improvement of intestinal pathological changes (100% in immunocompetent and 80% in immunosuppressed mice)[23].

The circumsporozoite protein (CSP), which is the major surface protein of *Plasmodia* sporozoites, is proteolytically processed by a parasite-derived cysteine protease and this event is temporally associated with sporozoite invasion of host cells. At low concentrations, allicin inhibited CSP processing and prevented sporozoite invasion of host cells *in vitro*. *In vivo*, mice injected with allicin had decreased *Plasmodia* infections compared to controls. Allicin was also tested on erythrocytic stages where a 4-day regimen of allicin administered either orally or intravenously significantly increased the survival of infected mice by 10 days[24].

In mice infected with *L. mexicana*, intraperitoneal injection of garlic extract or its protein fraction augmented parasite engulfment and destruction of intracellular amastigotes by macrophages. Modulation of the immune response through macrophages activations was postulated as a mechanism of action of garlic[25]. Another explanation claimed that garlic extract reduced macrophage infection through induction of nitric oxide (NO) production *in vitro*. Therefore, it may act on both T cells and macrophages to stimulate IFN-γ production and NO synthesis for parasite killing[26].

In a study conducted in 2007, *Eimeria stiedae* induced marked hepatic histopathological alterations in rabbits that were not treated with garlic, versus those treated with garlic. The effect of methanol garlic extract in a concentration of 3.90 mg/ml, on the growth of *Acanthamoeba castellanii* and its cytotoxicity on corneal cells was studied *in vitro*. These findings indicated its amoebicidal, as well as cysticidal effects on trophozoites and cysts, with no cytotoxicity to corneal cells[28]. In addition, aqueous garlic extract proved similar to metronidazole in inhibiting both multiplication and motility of *T. vaginalis*[13].

Antihelminthic effects: Aqueous garlic extract, with its potent free radical scavenging and antioxidant properties, seemed to be a highly promising agent in protecting hepatic tissue against oxidative damage due to *S. mansoni* infection[29]. Garlic efficacy was highest in the group treated with garlic before and after bilharzial infection and resulted in various ultrastructural alterations in the surviving adult worm's tegument[30]. Results of a study conducted in 2008 showed that chloroform garlic extract exerted the highest effect on the viability of hydatid cyst protoscoleces *in vitro*, in comparison with garlic aqueous extract and hydro-alcoholic garlic extract[31].

Garlic as repellent and its acaricidal effect: The repellent effect of garlic oil was evaluated against female *Phlebotomus* bite. A dose dependent anti-feeding effect, which was 100% effective at 1% concentration, was obtained[32]. Topical application of 10% garlic juice by spraying, effectively decreased Northern fowl mite (NFM, *Ornithonyssus sylviarum*) infestation in laying hens. Humans could be bitten by these mites and suffer irritation and allergic reactions[33].

Garlic as molluscicide: The effect of the plant-derived molluscicides *Annona squamosa* and *Lawsonia inermis* combined with *A. sativum* on the reproduction of the snail *Lymnaea* was studied. A significant reduction in the fecundity, hatchability and survival of young snails was observed[34].

***Artemisia* (Al-Sheeh)**

There are about 300 species in the *Artemisia* genus. Two of them, sweet annie (*Artemisia annua*) and wormwood (*Artemisia absinthium*), are of medical importance in treatment of some parasitic diseases. The active constituents in the first one are artesunate, dihydroartemisinin, artemether and arteether, while the second contains aromatic oils (thujone and isothujone) and strong bitter agents (absinthin and anabsinthin). Adverse effects associated with artemether treatment were abdominal pain, anorexia, nausea, vomiting, diarrhoea and CNS involvement (headache and dizziness)[35]. Longer-term use of wormwood (over 4 weeks) can cause nausea, vomiting, insomnia, restlessness, vertigo, tremors and seizures[36]. In addition, it is not recommended during pregnancy and breast-feeding[37].

Artemisinin (ART) derivatives: Mass drug administration schemes in malaria control should ideally use more than one drug, preferably combinations including a rapid-acting schizonticidal drug, such as ART, as well as primaquine that can kill sexual and liver stages to prevent transmission. This could be considered as an alternative strategy for malaria control, and in combination with other anti-malarial measures may provide a tool for malaria elimination and eradication[38]. ART combination therapy is the first-line treatment for uncomplicated *P. falciparum* malaria in most malaria-endemic countries[39]. All ART compounds induce very rapid reduction of parasitaemia, starting almost immediately after administration. The proposed mechanism of action involves cleavage of endoperoxide bridges by iron producing free radicals which damage biological macromolecules causing oxidative stress in parasitized cells[40]. Pure artemisinin has a low solubility in water, oil and therefore it could be administered orally, rectally and intramuscularly. Intramuscular artesunate is easier to administer but is associated with hypoglycaemia[41]. Unfortunately, oral administration is often not possible in patients with severe malaria, due to extreme vomiting; hence the development of several semi-synthetic ART derivatives[42].

Artemisinin also showed anti-leishmanial activity for both promastigotes and amastigotes and was accompanied by a high safety index. The leishmanicidal activity of artemisinin was mediated *via* apoptosis as evidenced by externalization of phosphatidylserine, loss of mitochondrial membrane potential and cell-cycle arrest. These data indicated promising anti-leishmanial activity mediated by programmed cell death[43].

Moreover, several ART derivatives were shown to be effective against *T. gondii in vitro*[44] as well as *in vivo* in a murine model of reactivated toxoplasmosis[45]. The mechanism of action is uncertain. However, it was suggested that they may inhibit sarcoplasmic-endoplasmic reticulum (ATPase), thus disrupting calcium homeostasis by increasing the periodicity of calcium oscillations and inducing recurrent, strong calcium spikes[44]. In addition, these new ART derivatives have the ability to inhibit multiple steps of *T. gondii* lytic cycle; they effectively inhibited *T. gondii* growth, tachyzoite replication, attachment to and invasion of host cells[46].

The ART derivatives were shown to possess a broad spectrum of activities against several helminthic infections. Combination between artemether and praziquantel showed highest efficacies against juvenile and adult worms of *S. haematobium*[47]. Scanning and transmission microscopic observations indicated that artemether induces extensive damage to juveniles and adults of different *Schistosoma spp.*[48]. In addition, significant progress has been made with artemether use for chemoprophylaxis in schistosomiasis, as immature stages of *S. mansoni* are more prone to oxidative killing than mature worms which probably participates in the mechanism of anti-schistosomal action of ART[49]. The efficacy and safety of artemether was studied in sheep infected with *Fasciola spp.* A single intramuscular dose of artemether significantly reduced both egg and worm burdens. There were no adverse events, however, two abortions were observed 7 days post treatment[50]. Recently, a study was carried out to determine the morphological changes to *F. hepatica* after *in vivo* treatment with artemether and the results showed increased disruption of the tegumental system, with isolated patches of surface blebbing and reduced production of secretory bodies by the tegumental cells[51].

Wormwood: *A. absinthium* extracts were found to be effective against the enteral (adult) and parenteral (larva) phases of trichinellosis[52]. In addition, oil extracts were tested in the laboratory against host-seeking nymphs of *Ixodes ricinus Linnaeus* (*Acari: Ixodidae*). The results showed 62-70% repellent ability and hence could be used in control of arthropods of medical, veterinary or agricultural importance[53].

***Commiphora molmol;* Myrrh (Al-Mor)**

All the three main constituents of myrrh; resin, gum and volatile oil are important in myrrh's activity as herbal medicine[54]. The mechanism of the anti-schistosomal action of myrrh on *S. mansoni* is not fully understood. However, it has been attributed to permanent muscle paralysis of the worms leading to their shift to the liver where destruction takes place[55]. Meanwhile, results of studies published on the efficacy of myrrh in the treatment of *S. mansoni*-infected mice are greatly conflicting. Several experimental and clinical studies reported significant parasite reductions and marked ultrastructural changes after treatment of *S. mansoni*-infected mice with Mirazid®[56,57] or under field conditions[58]. However, other studies negated myrrh efficacy in the treatment of schistosomiasis in either experimental[59], or clinical studies[60].

There is also such debate over the efficacy of Mirazid® for the treatment of fascioliasis. Complete cure rate was achieved in experimentally infected rabbits with oral dose of 20 mg/day for 6 consecutive days[61]. On the contrary, results obtained for experimentally infected sheep treated with Mirazid® appeared similar to those for untreated infected animals[62]. On the other hand, Mirazid® was reported to be effective against *D. dendriticum*[63], *H. heterophyes*[64] and *H. nana*[65]. Regarding its antiprotozoal efficacy, Mirazid® was effective against cryptosporidiosis[66] and trichomoniasis in metronidazole-resistant infected females[67].

Myrrh proved to have insecticidal activity against mosquito larvae of *Culex pipiens* and *Aedes caspius*[68]. In addition, the molluscicidal activity of myrrh was evaluated in several studies on *B. alexandrina*, *B. truncatus* and *L. cailliaudi* and the results revealed significant lethal and ovicidal effects[69,70].

***Curcuma longa*; Turmeric (Al-Korkom or Curcumin)**

As turmeric is a very cheap, easily available, effective and acceptable mode of treatment in developing countries, with no toxic or adverse reaction, it was used as paste for the treatment of scabies, with 97% cure rate within 3-15 days of treatment[71]. The active constituent known as curcumin showed a wide range of therapeutic actions. When used in the recommended amounts, turmeric is generally safe. Some herbal books recommend not taking high amounts of turmeric during pregnancy as it may cause uterine contractions and patients with gallstones or bile passages obstruction are advised to consult their healthcare practitioner before using turmeric[72].

Curcumin had a significant effect on the progression of experimental cerebral malaria. Survival of treated mice was significantly increased and development of cerebral malaria was either delayed or prevented[73]. Possessing antiprotozoal effects, turmeric as well proved to (1) show cytotoxicity against *T. brucei*[74], (2) have leishmanicidal activity *in vitro*[75], (3) inhibit *G. lamblia* trophozoite growth and adhesion, by more than 50%, in dose and time dependent manner[76] and (4) be an attenuating agent against *T. gondii* tachyzoites in the peritoneal fluid of mice[77].

Studies were designed to evaluate the schistosomicidal activity of curcumin *in vivo* as well as immuno-modulation of granulomatous inflammation in acute schistosomiasis *mansoni*. It was found that praziquantel was more effective in lowering worm burden while curcumin was more potent in reducing egg count[78]. The mechanism by which curcumin might function as a schistosomicidal agent is unclear and needs further investigation. In another study, curcumin was effective in reducing both male and female worms and tissue-egg burdens, hepatic granuloma volume and liver collagen content. In addition, curcumin treatment modulates cellular and humoral immune responses of infected mice[79]. On the other hand, curcumin is effective in the treatment of many inflammatory diseases. Its efficacy on reducing the histopathological changes of opisthorchiasis in hamsters was evaluated. Results showed reduced inflammatory cells aggregation surrounding the hepatic bile ducts, leading to reduced risk factors of cholangiocarcinoma development[80]. For molluscicidal activity, turmeric was evaluated against *B. alexandrina* and the results showed that its 30 ppm extract stopped snail egg laying and caused deformity of all embryonic stages[81].

***Nigella sativa; Nigella* (Black Seed or Habbat Al-Barakah)**

Nigella oil contains saponin, nigellidine and nigellone and its seeds contain thymoquinone, monoterpenes such as p-cymene and α-pinene[82]. Several mechanisms were described for the activity of black seeds such as its protection against hepatotoxicity[83], its antioxidant role[84] and stimulation of immune system[85]. The results of the studies conducted in 2007 proved that its aqueous extract could be useful in the treatment of *B. hominis*[86] and as an anti-malarial drug[3]. In the following year, its inhibitory effect against *T. vaginalis* was investigated *in vitro* and the results showed remarkable inhibition of trophozoites growth and motility[87].

The antioxidant and anti-schistosomal activities of *N. sativa* oil was studied in control and *S. mansoni*-infected mice. Remarkable reduction in worms, tissue eggs and alteration in oogram pattern were recorded in all the treated groups. The data pointed to the importance of these seeds as a promising agent to complement schistosomiasis specific treatment[29]. Its antiparasitic effect was studied also in *H. nana*-infected mice, where it was found to reduce the infection starting from 2nd day of the treatment[85]. Moreover, its prophylactic treatment prior to *T. spiralis* infection was effective against both adult worms and muscle larval count in infected rats[14].

***Zingiber officinale;* Ginger (Ganzabil)**

The main constituents of ginger are the gingerols, shogaols, zingerone and paradol[88]. The anti-amoebic effect of a crude drug formulation against *E. histolytica* was studied in comparison to metronidazole. Results showed that the product had a minimal inhibitory concentration of 1000 mg/ml as compared with 10 mg/ml for metronidazole[89]. *In vitro*, a concentration of 200 mg of ginger extract killed almost all *Schistosoma* worms within 24 hrs[90]. The anti-helminthic activity of ginger was reported also in sheep naturally infected with mixed species of GIT nematodes e.g. *T. colubriformis, Strongyloides papillosus and Trichuris ovis*[91]. Another study conducted in 2006 showed that there was significant reduction in intestinal adult worms and muscle larval count in mice infected with *T. Spiralis*[92]. In addition, there was microfilaricidal activity of aqueous extracts of ginger when administered to dogs infected with *D. immitis* filarids[93].

Ginger essential oils proved to have repellent results against host-seeking chiggers (scrub typhus) of *Leptotrombidium imphalum*[94] and ovicidal and repellent effects against different mosquitoes as *Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus*[95]. In addition, its petroleum ether extract has larvicidal activity against *A. aegypti* and *C. Quinquefasciatus*[96].

As a molluscicidal agent, gingerol and shogaol exhibited potent effects on *Biomphalaria glabrata*, indicating their ability to interrupt *Schistosoma* transmission[97]. Results of *in vivo* exposure of *Lymnaea acuminata* to gingerol proved its effect on snail neurotransmission mechanisms, either separately or through a complex interaction between the different neurotransmitters[98].

Berberis vulgaris, Berberis Aristata; **Barberry**

The active constituent in barberry is berberine which is an alkaloid having antibacterial, anti-amoebic, anti-fungal, anti-helminthic and leishmanicidal properties. Its reported main side effect was interference with normal liver function in infants. Strong standardized extracts may cause stomach upset and should be used for no more than two weeks continuously. Other symptoms of excessive berberine intake include lethargy, nose bleed, skin and eye irritation and kidney irritation[71].

Berberine is a useful drug for the treatment of visceral as well as cutaneous leishmaniasis. In *L. donovani* infection, it inhibited *in vitro* multiplication of amastigotes in macrophage culture and their transformation to promastigotes in cell free culture[99], while 1% berberine sulphate inoculated intra-lesionally was found to be highly effective against cutaneous leishmaniasis in domestic dogs[100]. In addition, crude extract formulation including berberine had a maximum cure rate of 73% at a dose of 800 mg/kg/day in hepatic amoebiasis[101]. The results of a study conducted in patients with chloroquine-resistant malaria indicated that berberine was more effective in clearing the parasite than both tetracycline and cotrimoxazole and that the combination of pyrimethamine and berberine gave the best results for chloroquine resistant malaria[102]. Moreoyer, berberine sulphate was comparable to metronidazole as regards potency on the growth of *T. vaginalis in vitro*[103].

Azadirachta indica, Melia Azadirachta; **Neem**

The major active constituents in neem are fatty acids and terpenoids such as azadirachtin, which is considered to possess anti-microbial and insect repellent effects, among many other actions[104]. Neem seed oil is problematic and should be kept out of reach of children[105]. In this form, it is mainly used in control of vector borne parasitic diseases. The larvicidal and emergence inhibitory activities of neem were tested successfully against the vectors of malaria, filariasis and dengue fever[106]. Besides, water-free neem seed extract shampoo was effective against *S. scabiei*-infesting dogs in Egypt[107]. As an acaricidal agent, neem extracts showed high level of efficacy (80%) for adult ticks after 5 hours of treatment[108]. As a pediculicide, its extract shampoo proved to be highly effective against all stages of head lice, with no side effects[109]. The significant repellent activities of neem against *Phlebotomus papatasi*[110] and *Ixodes ricinus*[111] nymphs were reported.

Cinchona officinalis; **Cinchona (Al-Quina tree)**

The medicinally active constituents of cinchona are a variety of alkaloids as quinine and quinidine. Oral quinine has marked side effects, including tinnitus, dizziness and nausea[112]. Quinine has been used as malaria treatment for more than 350 years in Africa and remains the first-line anti-malarial drug for the treatment of complicated malaria in Europe and Africa. Children with uncomplicated malaria are generally treated with oral medication, except those unable to take oral drugs[113]. It has substantial disadvantages mainly its poor tolerability, the long treatment course and the unpleasant bitter taste of its tablets[114]. Therefore, it is no longer recommended by the WHO as first line treatment for malaria and should be used only when artemesinins are not available[115]. Treatment of *S. mansoni*-infected female mice with daily intraperitoneal injections of quinine and quinidine caused significant decrease in worm burden and egg production. Their schistosomicidal effects are due to their capacity to interfere with hemozoin formation which is the main heme detoxification pathway in *S. mansoni*[116]. In addition, quinine and chloroquine are considered potential drugs against *L. loa* infection[117].

Triticum vulgare, Triticum aestivum; **Wheat germ (Ganin Habit Al-Kamh)**

Lectin (wheat germ agglutinin) is the active constituent, however, it is a concentrated source of vitamin E, folic acid, phosphorus, thiamin, zinc and magnesium, as well as essential fatty acids and fatty alcohols[71]. In a clinical trial, wheat germ helped in quick resolution of symptoms in *Giardia*-infected patients. It did not kill the parasites, but prevented their growth, replication and attachment[118]. In addition, the effectiveness of wheat germ as a useful dietary supplement administered to *E. histolytica*-infected patients was reported, both in acute and chronic stages of infection[119]. When its therapeutic effect was experimentally evaluated in immunosuppressed mice infected with *Cryptosporidium* oocysts, it showed significant reduction of excreted oocysts on day 7 post-infection[120]. It was also shown to have remarkable inhibitory effect on multiplication and motility of *T. Vaginalis*[87].

Cinnamonum zeylanicum; **Cinnamon (Al-Kerfa)**

Various terpenoids (eugenol and cinnamaldehyde) are believed to account for cinnamon's medicinal effects[121]. Some people develop bronchial constriction or skin rash after exposure to cinnamon and chronic use of the concentrated oil may cause mouth inflammation. Cinnamon is not recommended for use by pregnant women[71]. Cinnamon essential oil had potent insecticidal and ovicidal activities against human head louse, *P. humanus capitis*[122], acaricidal activity against adult *Dermanyssus gallinae*[123] and strong larvicidal activity against 4th instar *Aedes aegypti* larvae[124]. Recently, its inhibitory action against other mosquito species as *Aedes albopictus*, *Culex quinquefasciatus* and *Armigeres subalbatus* larvae was reported[125].

Melaleuca alternifolia; **Tea Tree:**
Oil of tea tree containing terpenoids such as terpinen-4-ol and cineole has the ability to kill resistant fungus and bacteria[126]. The reported side effects included burning and allergic reactions[127]. Its oil was reported to have similar repellent effects, as clove oil used against scrub typhus[94]. Tea tree oil (5%) showed similar effects as those of benzyl benzoate, lindane and ivermectin against all stages of *S. scabiei*[128]. Acaricidal and pediculocidal activity against house dust mites and lice was evaluated using three essential oils: Tea tree, lavender and lemon and the results revealed that tea tree oil was the most effective[129]. Moreover, improvement of symptoms and dramatic resolution of ocular irritation and conjunctival inflammation were reported in patients with *Demodex* blepharitis who were treated with 50% tea tree oil shampoo for a minimum of 6 weeks[130].

Cucurbita pepo, Cucurbita maxima; **Pumpkin (Karh El-Asal, or Al-Yakten):**
Pumpkin seeds contain several active constituents: Essential fatty acids, amino acids, phytosterols (e.g. β-sitosterol), minerals, vitamins and curcurbitin which shows anti-parasitic activity[131]. Oral administration of crude ethanolic extracts from *C. maxima* reduced by 50% the levels of parasitaemia in *Plasmodium berghei*-infected mice[132]. In heterophyiasis, a combined extract of areca nut and pumpkin seeds gave an excellent result than when either extract was given alone[133]. In addition, it gave effective results against canine tapeworms[134]. Its leaf extract with different solvents showed larvicidal, ovicidal and repellent activities against *Culex quinquefasciatus*[135].

Less Commonly Used Herbal Medicine with Antiparasitic Effects

Cuminum cyminum; **Cumin (Al-Kammoun):** Cuminaldehyde, cymene and terpenoids are the major constituents of volatile oils of cumin[136]. It is usually used in traditional medicine as a stimulant, a carminative and an astringent[137]. Significant larvicidal activity (100% mortality) of essential oils derived from cumin against early 4th stage larvae of *Aedes aegypti* and *Culex pipiens* was reported[138].

Eugenia caryophyllata; Syzygium aromaticum **Clove (Al-Kornfel):** The main constituents of the clove essential oil are phenylpropanoids such as carvacrol, thymol, eugenol and cinnamaldehyde[139]. Under field conditions, Gel B (20% clove oil) provided significant repellent effects against *Aedes aegypti*, *Culex quinquefasciatus* and *Mansonia uniformis*. These promising results raised the possibility for its use by low-income rural communities against various mosquito species[140]. Moreover, essential oils of clove showed repellent effects against host-seeking chiggers (scrub typhus) of *Leptotrombidium imphalum*[94].

Pimpinella anisum; **Anise (Al-Yanson):** The active constituents in anise, particularly the terpenoid anethole, are in its volatile oil[141]. Its uses for medication in parasitic diseases are due to its insecticidal and repellent effects. The acaricidal activity of anise seed oil against house dust mites *Dermatophagoides farinae* and *D. pteronyssinus* was about 8.4 and 6.7 times more toxic than benzyl benzoate, respectively[142]. Besides its acaricidal activity, it was highly effective as both larvicidal and ovicidal against different mosquito spp. As *Anopheles, Aedes* and *Culex*[95]. Moreover, its spray preparation had significant cure rates against head louse infestations[143].

Punica granatum; **Pomegranate (Al-Roman):** Ellagic acid is likely to be the main constituent responsible for the antiparasitic effect of pomegranate[144]. It acts through stimulation of the cell-mediated and humoral components of the immune system[145]. The *in vitro* studies conducted in 2009 proved that ellagic acid may contribute as a promising anti-malarial drug[146], it had the ability to inhibit the growth of *P. falciparum* asexual blood stages *in vitro*[147]. In addition, a natural plant extract purified from pomegranate was effective against *T. vaginalis in vitro*[67].

Ricinus communis; **Castor Oil Plant (El-Khirwa):** Ricinoleic acid is the main component of castor oil, and it constitutes approximately 90% of its fatty acid content[148]. Leaves of castor oil plant are toxic to sand flies and offer protection against their bites and decrease the risk of leishmaniasis[149]. The methanol extract of castor oil exhibited acaricidal and insecticidal activities against *Haemaphysalis bispinosa* and *Hippobosca maculata*[158].

Rosmarinus officinalis; **Rosemary (Ekleel Al-Gabal):** The active constituents include volatile oil (eucalyptol or cineole) as a potent antibacterial agent, rosmarinic acid with antioxidant activity and carnosol as anti-cancer formation in animal studies. Internal intake of its oil should be avoided during pregnancy because it may cause abortion[151]. Rosemary oil produced decreased oviposition, had high larvicidal activity against all larval stages of *A. aegypti* and proved to be a promising agent in mosquito control programs[152]

Salix alba; **Willow (Al-Sefsaf):** The main active constituent is glycoside salicin which has anti-inflammatory and pain-relieving actions. As with aspirin, some people may experience stomach upset from taking willow[153]. During the American Civil War, the unreliable supply and high cost of quinine forced the Confederate Army to use alternative treatments for malaria which were made from indigenous plants such as dogwood, willow and tulip tree. The quinine substitutes were generally considered useful but not as effective as quinine[154].

Thymus vulgaris; **Thyme (Al-Zaatar):** The primary constituents are the volatile oils, including phenols, thymol and carvacol. Thyme oil should be reserved for topical

use, as internally it may lead to dizziness, vomiting and breathing difficulties[151]. So, its hydroalcoholic extract was significantly effective in reduction of ulcer size in cutaneous leishmaniasis[155]. Its volatile oil was effective against *Lucilia sericata* 3rd stage larvae[156] and *Pediculus humanus*[157].

Herbal Medicine with Limited Molluscicidal Effects

***Ambrosia maritima* (Damsissa):** In a field trial in Egypt, the possible use of single annual application of damsissa plant, in snail control program for schistosomiasis transmission season in Lower Egypt, was suggested[158]. Longer prepatent period and remarkable decrease in cercarial production was also recorded in snails treated with the sublethal concentrations of this molluscicide[159]. In addition, it has lethal effects on *Lymnaea* snails[160].

Azolla pinnata: Molluscicidal activity of *A. pinnata* was reported against *B. alexandrina* snails. Its ethanol extract, at 6600 ppm for three hours exposure, killed 100% and 19.4% of *S. mansoni* miracidia and cercariae, respectively[161].

***Euphorbia spp.* (Sabbaar):** The physiological and lethal effects of the latex components of *E. splendens*[162]and *E. milii*[163], on *Biomphalaria spp.* were reported. It was found that unfiltered crude latex extract is a more potent molluscicide than filtered latex[162] and milin (the active component) is likely to be responsible for alteration of normal physiological functions and lethality of snails[163].

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