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Literature Review: *Punica granatum* (pomegranate) with an emphasis on its anti-parasitic activity

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Abstract

The pomegranate (*Punica granatum*) has been known for its medicinal and nutritional benefits from time immemorial and across ancient civilizations. In addition, people of numerous civilizations have known pomegranate since ancient times (4000–3000 B.C.). Pursuant to one source; it was cultivated for the first time in Iran; while another claimed it was in India or Turkey. Then it was expanded along trade routes to reach each region of the entire world. The pomegranate was highlighted in this study through a literature review in terms of its origin, classification, and description; its medicinal and therapeutic significance; the chemical content of the various pomegranate parts; and lastly, its antiparasitic activities. Pomegranate belongs to the *Punicaceae* family. Interestingly, it has been frequently employed in disease therapy since ancient times. Furthermore, pomegranate fruits, seeds, and peels are frequently utilized as a natural remedy in traditional medicine. Flavonoids, ellagitannins, punicalagins, ellagic acid, vitamins, minerals are the most significant ingredients in this plant. Researchers have been evaluating the fruit's characteristics in recent years and have revealed encouraging findings in areas such as cardiovascular health, cancer prevention, anti-inflammatory, and antimicrobial activities. The pomegranate's unique blend of antioxidants, polyphenols, and other bioactive chemicals has been demonstrated to benefit several areas of human health. In this review, the researcher highlighted the substantial role of the pomegranate as an antiparasitic agent by reviewing numerous studies performed on this topic, whether *in vitro* or *in vivo*. Despite a scarcity of research to evaluate its anti-parasitic properties, this study concluded that the pomegranate has anti-parasitic properties that are very encouraging, such as anti-amoebic, anti-anthelmintic, cryptosporicidal, leishmanicidal, giardiacial, and other anti-parasitic characteristics.

Keywords: Pomegranate; Chemical constituents; Medical significance; Anti-parasitic activity; Pomegranate extracts; Literature Review

1 Introduction

Punica granatum (pomegranate) is one of the first edible fruits discovered. It has long been used in traditional medicine in America, Asia, Africa, and Europe to treat a variety of diseases. Pomegranate has been reported to be useful in lowering inflammation and enhancing heart health due to its high antioxidant content. In addition, it is utilized in contemporary medicine and has anti-cancer characteristics. Furthermore, it has been observed to improve memory and cognitive performance in older people, as well as help with diabetes management and the prevention of some diseases. Overall, utilizing pomegranate in a healthy diet can provide several health benefits [1]. Moreover, in Ayurvedic medicine, pomegranate is regarded as "a pharmacy unto itself" and is utilized as an anti-parasitic agent, a "blood tonic," and to cure aphthae ulcers [2]. It should be mentioned that the pomegranate is one of the earliest fruits known to humankind, as numerous historical records claim that it was one of the first five crops to be farmed, along with figs, dates, olives, and grapes. Moreover, it has been recognized for its therapeutic characteristics for ages and is a rich source of antioxidants, vitamins, and minerals. Humans began to cultivate it between 3000 and 4000 BC in northern Iran and

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Turkey. Nowadays, it is commonly consumed in a variety of forms across the world, including juice, jam, and as a garnish in salads and other cuisines [3]. It spread from there to other regions, including the Mediterranean countries, India, and China, most likely through historic trade routes. Pomegranate cultivation and consumption have a long history in human history, with numerous ancient tribes employing it as a food source and a medical cure. For instance, it was used in ancient medicine in Ayurvedic scriptures to cure several diseases such as diarrhea and inflammation. Furthermore, ancient civilizations such as the Persian and Egyptian civilizations used the fruit's symbolism and connotations with fertility and wealth in religious rites and artworks [4]. In contrast to the aforementioned, some claim that the pomegranate originated in Iran and northern India, not Turkey, and that it has been grown across the Mediterranean region for thousands of years. Various environmental factors influence flavor, color, antioxidant capability, and chemical composition. There are also other pomegranate varietals, each with its own distinct qualities. The Hicaz type, for instance, is recognized for its big size and rich red color, but the Mollar de Elche variation has a softer texture and a sweeter taste. Because of these discrepancies in flavor and appearance, the pomegranate is a versatile fruit that may be utilized for a number of culinary applications [5, 6]. Contrariwise, to all of the aforementioned, others believe that the pomegranate originated in the Mediterranean region and crossed from there to the Indian continent, where it was utilized in traditional medicine and in a variety of other countries throughout the world. It is worth mentioning that the pomegranate gets its name from the Latin words "*ponus*" and "*granatus*" [7].

2 Morphology and classification

Pomegranate is a shrub with multiple stems that may grow from 1.8 to 4.6 meters in length, with light green, deciduous, and brightly colored leaves that measure 7.6 cm in length. The flowers are massive, lustrous orange to scarlet in color, trumpet-shaped with petals, and around 5 cm long. Because it is generated over a lengthy period throughout the summer, it is usually doubled. Subsequently, the fruit is an 8–12 cm-diameter spherical to lower sphere with a stiff tubular calyx and a leathery covering that is lustrous red to yellowish-green in color and laden with crunchy seeds that are each wrapped in a membranous skin [8, 9]. Moreover, pomegranate (*P. granatum*) is also a fruit-bearing deciduous shrub or small tree that grows between 5 and 8 meters tall. Pomegranate fruit is generally crimson, spherical, and roughly the size of an apple. It has juicy arils, which are little edible seeds surrounded by a luscious pulp [10, 11, 12]. Table 1 below is an illustration of its systematic classification.

Table 1 Systematic classification of pomegranate [13]

Kingdom	***Plantae* – Plants**
Subkingdom	*Tracheobionta* – Vascular plants
Super division	*Spermatophyta* – Seed plants
Division	*Magnoliophyta* – Flowering plants
Class	*Magnoliopsida* – Dicotyledons
Subclass	*Rosidae*
Order	*Myrtales*
Family	*Punicaceae* - Pomegranate family
Genus	*Punica* L. - pomegranate
Species	*Punicagranatum* L. - pomegranate

3 Chemical constituents

Astonishingly, all of the parts of the pomegranate contain a wide range of essential medicinal and nutritional elements. Alkaloids can be found in the root, tree bark, and fruit peel, among other places. Pomegranate seeds and juice are also rich in antioxidants like polyphenols. Additionally, the fruit is high in vitamin C, vitamin K, and potassium, all of which are essential for good health [14, 15]. On the other hand, the pomegranate seed consists primarily of hydroxybenzoic acid. Sterols, tocopherols, triterpenes, isoflavones, phenyl aliphatic glycosides, conjugated fatty acids, non-conjugated fatty acids, and lignins [16].While pomegranate bark is primarily composed of ellagitannins, including punicalin and punicalagin, as well as numerous piperidine alkaloids, the most therapeutically beneficial pomegranate constituents are ellagic acid, ellagitannins (including punicalagins), punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavonols and flavones [2]. Eventually, *P. granatum* constituents showing therapeutic activities include

gallocatechins, delphinidin, cyanidin, gallic acid, ellagicacid, pelargonidin, and sitosterol [97]. The rinds contain the alkaloids pelletietine (C8H15ON) and tannin [9]. While table (2) below demonstrates the chemical composition of the pomegranate parts in brief.

Table 2 The chemical composition of the different pomegranate parts

Plant part	Chemical constitute	References
Peels	flavonoids, ellagitannins and proanthocyanidin compounds and minerals such as calcium, magnesium, phosphorus, potassium and sodium. Alkaloids	[14, 15, 17]
seeds	Oil, octadecatrienoic fatty acids, triacylglycerols, lignins, hydroxycinnamic acids, punic acid, linoleic, oleic, palmitic , stearic acid, tocopherols, sterols, sex sterodides, gallic acid and ellagic acid, protein, crude fibers, vitamins, minerals, sugars, polyphenols, the phytoestrogen coumestrolestrone, Alkaloids.	[18, 19] [14, 15]
Juice	Water, sugars, pectin, polyphenols, fatty acids, sterols, triterpenoids, tocopherol, Anthocyanins, flavonoids, Minerals, catechins, proanthocyanidins, quercetin and elagitannins, Alkaloids	[16, 18] [14, 15]
Flowers	Gallic acid, ursolic acid, terpenic compounds, maslinic acid, Asian acid, oleanolic acid flavonoids, tannins, catechin, anthocyanins,	[18, 20] [14, 15]
Leaves	Tannins, apigenin, flavones, naringin, punicalinas, punicalaginas, punicafolina, potassium, calcium, iron, magnesium, zinc, saponins, anthocyanins, alkaloids,	[18, 21]

4 Medical significance of pomegranate

The pomegranate is without a doubt one of the oldest plants used as medicine since antiquity, as evidenced by the numerous digestive system disorders and skin diseases for which it has been employed as a therapy. In addition, it has become known as a "super food" in recent years because of its high antioxidant content, which is thought to aid the body in fighting numerous diseases. Its antioxidant properties have been associated with a lower incidence of Alzheimer's disease, cancer, and heart diseases. Pomegranate has also been revealed to contain anti-inflammatory components that may mitigate the signs and symptoms of arthritis and other inflammatory disorders. The purported health advantages of the fruit have inspired the creation of several pomegranate-based nutritional supplements and cosmetic items [15, 22, 23]. Despite the significance of antibiotics as a scientific revolution that clearly contributed to the reduction of the impact of infectious diseases, the recent increase in drug-resistant microbial infections and the spread of global epidemics have shed light on medicinal plants as an alternative natural medicine, with the pomegranate receiving recent attention. Furthermore, studies have shown that pomegranate may be used as a natural alternative against a variety of microbial infections and as a substantial medicinal agent with a variety of therapeutic indications. Numerous studies conducted on this topic practically across the globe showed this impressively [24, 25]. While consumers throughout the world are becoming more interested in foods that promote health as they become more aware of the linkages between food and health [27]. In addition to aesthetic beauty [27], hormone replacement treatment [28], and allergy relief [29, 30. 33], mouth wash [32], ophthalmic ointment [15, 31], weight loss soap [34], and as an adjuvant therapy to increase radioactive dye bioavailability during diagnostic imaging [35], pomegranate-derived medicines are being used to treat acquired immune deficiency syndrome (AIDS) [28]. The most well known utilization has been as a vermifuge or taenicidal agent [36, 37], that is, a killer and expeller of intestinal worms., on the On another hand, it has potent antioxidant and anti-inflammatory properties. When used to treat diarrhea, Calzada et al. (2006) reported that *P. granatum* had an antiprotozoal chemotherapeutic effect against *E. histolytica* and *G. lamblia* in Mexican traditional medicine [38]. Furthermore, Amorin et al. (2003) reported that *P. granatum* extracts have anti-schistosomal activity in a mouse model [35]. Besides, Toklu et al. (2007) observed that injection of *P. granatum* rind extract reduced oxidative damage in the liver and enhanced hepatic structure and function, in addition to antiparasitic activity [39]. Adhami and Mukhtar (2007) defined *P. granatum's* use as a dietary antioxidant for cancer chemoprevention [40]. In the cosmetic industry, rind powder is used as a tooth powder as well as a medication. Rind powder is high in beta-carotene, potassium, phosphorus, and calcium. Moreover, the rind is used in folk medicine because of its great astringency, making it a popular therapy all over the world in the form of an aqueous decoction (boiling the hulls in water for 10–40 minutes) for dysentery and diarrhea, as well as stomatitis [10, 11].

5 Anti-Parasitic Activity of pomegranate

Parasitic infections have long been a serious global issue, particularly in overcrowded countries and societies with poor infrastructure. Moreover, as time passes, parasites resistance to medications in general rises, aggravating the situation and making the treatments less effective. Therefore, it raised the worldwide economic burden, and there is no doubt that all of these circumstances made the creation of new pharmaceuticals from medicinal plants critical. Furthermore, the pomegranate is regarded as one of the most significant of these plants to study and use, as many parts of it, including roots, bark, stem, and peels, have been utilized as vermifugal and taenicide agents [41, 42]. Pomegranate has been used as an antiparasitic since ancient times, with the ancient Egyptians using it to cure tapeworms and other parasites, as well as numerous ancient civilizations using pomegranate to treat diarrhea and dysentery [43, 44]. Because of its anti-microbial characteristics, pomegranate has been used for ages to cure diarrhea and dysentery. While investigations have shown that it can be useful in combating dangerous germs, research on its anti-parasitic activity is currently restricted and has to be expanded. In addition, it is high in antioxidants and anti-inflammatory substances, which have been demonstrated to offer several health advantages in addition to their anti-microbial properties [45, 46].

5.1 Hymenolepis nana

The dwarf tapeworm, *H. nana*, is the ubiquitous human tapeworm, according to numerous studies. It is believed that up to 75 million human beings are carriers, with infection rates among children reaching 25% in some regions. *H. nana*, on the other hand, is exceptional among tapeworms in that it may complete its life cycle without the requirement of an intermediate host. Not only that, but self-infection can last for years, causing a major economic and parasitological burden, particularly in immunocompromised hosts. The infection, however, is normally limited to the digestive tract and does not spread to other places. When adult tapeworms hatch in the small intestine, the embryos (oncospheres) penetrate the host intestinal villi and convert into larvae (cysticercoids) before breaking out and reattaching to the mucosal lining. Symptoms of a tapeworm infection may include abdominal pain, diarrhea, and weight loss. Treatment typically involves medication to kill the tapeworms and careful hygiene to prevent re-infection [47, 48].

5.1.1 *Anti-Hymenolepis nana activity of Pomegranate extracts*

In the Kingdom of Saudi Arabia, Al-Megrin conducted one of the most fascinating studies on the impact of pomegranate peel extract on *H. nana* in 2016. Pursuant to her study's findings, employing pomegranate peel extract decreased the quantity of parasite eggs excreted by infected mice when compared to the control group. In her investigation, 28 *Swiss albino* mice were infected spontaneously with *H. nana*. Later, the infected animals were separated into four groups: the first was the control group, and the other three were fed daily dosages of 0.5 ml, 1.0 ml, and 1.5 ml of pomegranate peel extract at a concentration of (300 mg /kg), respectively. The researcher, on the other hand, counted eggs in grams (EPG) one day before treatment and on days; one, seven, fourteen, and twenty-one after the treatment, following which all animals were euthanized on day twenty-one. The researcher counted and inspected the contents of the intestines for the existence of worms. Astonishingly, according to the findings of her investigation, the researcher determined that pomegranate peel extract decreased egg production in the infected groups' fecal pellets compared to the control group. As a result, the researcher believes that pomegranate peel extract might be used as a natural anthelmintic against *H. nana* infection in mice [49]. In another study, a group of white albino mice was inoculated with human feces containing *H. nana* eggs at a concentration of 100 eggs per mg. Then they were treated with pomegranate peel extract after infection, and the study concluded that pomegranate peels produced a substantial drop in the number of viable eggs after 7 days of treatment compared to the first day. Pomegranate peels have anthelmintic activity against *H. nana*; therefore, they may be utilized as an alternative, cheaper, and safer therapeutic protocol in the treatment of *H. nana* infection [50].

5.2 Schistosoma

Schistosomiasis is a parasitic disease caused by *Schistosoma* flukes; in addition, it infects at least 230 million humans globally, according to conservative estimates. Adult schistosomiasis worms may survive in human blood vessels for years, avoiding the immune system while producing hundreds of eggs daily, which either leave the body in the droppings or get stuck in surrounding tissues. Schistosomiasis is a chronic disease that can harm internal organs and impede children's growth and cognitive development. The disease is widespread in a number of developing countries, notably Sub-Saharan Africa, where clean water and sanitation are scarce [51].

5.2.1 Anthelmintic activity of Pomegranate against Schistosoma mansoni

In addition, studies on *Schistosoma mansoni* (*S. mansoni*), one of the three main species that infect humans, were carried out *in vitro* and *in vivo* by Fahmy et al. (2009). Both mature *S. mansoni* worms and schistosomules were strongly impacted by pomegranate peel and leaves extracts, which had 100% mortality rate after 24 hours of exposure. However, oral treatment of mice with the pomegranate extract at a concentration of 800 mg/kg for 45 days after infection and on three successive days resulted in a high proportion of adult worms that were dead (77.30 and 72.2%), depending on whether the extract was from the leaves or the peels [52]. Further researches are recommended to evaluate the effectiveness of pomegranate extracts in treating schistosomiasis in humans; however, these findings point to them as a potentially effective natural therapy alternative. Investigating the active ingredients responsible for the anti-schistosomal activity that has been detected would also be intriguing. Moreover, the findings of another study indicated that pomegranate peel extract had a good, effective, and deadly impact on *Schistosoma* adult worms, with more than 72% of the overall worms treated with pomegranate peel [53]. Pomegranate extracts have demonstrated anti-schistosomiasis activity against *S. mansoni*. Furthermore, because of diminished or lost motor activity, death, and superficial morphological abnormalities in mature worms, schistosomiasis treatment is a possibility. Similarly, the research suggests that pomegranates might be a viable option for the development of revolutionary schistosomiasis therapeutics [54].

5.3 Giardia lamblia

G. lamblia is a zoonotic parasite. It multiplies in the small intestine of vertebrate hosts, causing the diarrheal disease known as giardiasis. Fascinatingly, almost all mammals can be infected with *G. lamblia*. Moreover, epidemiological data refer to giardiasis as a zoonotic disease. Infections with this parasite vary; for instance, in humans, they may be asymptomatic or associated with diarrhea, malabsorption, and bloating, abdominal pain, fatigue, and weight loss. Based on the latest figures provided by the World Health Organization, *G. lamblia* is the third most common agent of diarrheal disease worldwide, with more than 300 million cases reported annually among children under the age of five [55, 56].

5.3.1 Anti- Giardia lamblia activity of Pomegranate extracts

Several investigations on the effect of pomegranate peel extract on protozoa have also been implemented. In one study, Al-Megrin discovered that on the tenth day of ingesting pomegranate peel extract, the cure rate of giardiasis had reached 50% among the experimental groups of mice, while the incidence of cysts in stool had decreased significantly. By the twentieth day of utilizing the extract, recorded rates had reached 75%, and by the twenty-eighth day of extract therapy, the cure rate of giardiasis in this group had reached 97.4% [57]. El-Kady and her colleagues, on the other hand, did a research in which they investigated the antiparasitic impact of *P. granatum* (pomegranate) and evaluated its therapeutic efficiency in *G. lamblia*-infected rats. An *in vitro* investigation revealed that the ethanolic extract of pomegranate peel was highly effective in destroying *G. lamblia* cysts, as evidenced by eosin vital staining. The *in vivo* investigation also revealed that pomegranate extract dramatically decreased the amount of *G. lamblia* trophozoites and cysts in infected rats' small intestine. These data imply that pomegranate might be a natural treatment for *G. lamblia* infections. Intriguingly, the number of *G. lamblia* trophozoites and cysts in the pomegranate extract-treated group was considerably lower than in the metronidazole-positive control group [58]. These findings indicate that pomegranate peel extract may be a viable natural therapy for giardiasis in humans, but trials that are more clinical are needed to establish its efficacy. Furthermore**,** the previous studies emphasized the potential of natural therapies in the treatment of parasitic diseases.

5.4 Plasmodium falciparum

Tropical malaria, which is a vector-borne infectious disease, is caused by *P. falciparum*. Take into account that a half million deaths are reportedly attributable to it worldwide to fully realize its significance to public health. This parasite is classified as an obligatory intracellular parasite as well. According to certain statistics and estimations, 2.2 billion people worldwide were at risk of contracting *P. falciparum* in 2002, with Africa being the endemic region, followed by highly populated areas in Southeast Asia. Female *Anopheles* mosquitoes, which transmit the parasite and infect people with their bites, facilitate the dissemination of this disease. Malaria symptoms include fever, headache, chills, and vomiting, and if ignored, they can result in serious consequences such as anemia, respiratory distress, and organ failure [59, 60].

5.4.1 Antilasmodial activity of Pomegranate

People have been interested in pomegranate as an anti-malarial from time immemorial because this disease, as previously mentioned, is regarded as a threat to public health as well as a worldwide burden. From there, the focus shifted to alternative medicine in the treatment of this ailment. The most notable of them are pomegranate gallagic acid

and punicalagin, both of which have demonstrated significant antiplasmodial activity against *P. falciparum* [61, 62]. These data imply that pomegranate may be a potential natural medicine for malaria treatment and prevention. Nevertheless, further studies are needed to determine the appropriate dose and efficacy in humans. Moreover, Al-Musayyib and colleagues conducted a remarkable study in which they investigated the anti-protozoal activity of 16 Saudi medicinal plants, including pomegranate and *P. falciparum*. Their findings also revealed that pomegranate peel methanolic extract was one of the most therapeutic plants with anti-parasitic properties. Therefore, the results showed that the IC_{50} was found to be 6.7 µg/ml [63], and their study also showed that pomegranate is still used as a home remedy for malaria in India and is believed to successfully contribute to the control of this disease [63, 64, 65].Furthermore, it should be emphasized that *P. granatum's* antiplasmodial effect is related to various significant chemical components in pomegranate rind, the most significant of which are ellagic acid and punicalagin. By interrupting its metabolic pathways and producing oxidative stress, ellagic acid and punicalagin have been proven to suppress the growth of *P. falciparum*, the parasite responsible for malaria. These findings suggest that pomegranate rind may be a source of natural anti-malarial agents [66]. Mubaraki and his colleagues did a somewhat different investigation that verified the results of the aforementioned Saudi study's study, but it ultimately confirmed the results of the Saudi study since their study was *in vivo*. The parasite and pomegranate rind extract were injected into experimental mice as part of their investigation. After 6 days of infection, the mice were euthanized and the relevant tests were performed on them, resulting in the conclusion that pomegranate rinds demonstrated a substantial antimalarial activity in the host by lowering inflammatory and oxidative stress responses. Besides, according to their findings, pomegranate improved the host's innate immune response. Their study, like the previous one, suggested that pomegranate rind may be used as an alternate therapy to reduce clinical episodes of malaria and may even avoid the infection [67]. Moreover, numerous studies have been conducted that support the use of pomegranate peels, notably as an antimalarial drug. Recent investigations have illustrated that pomegranate peels contain chemicals that can limit the development of the malaria parasite, making them an intriguing natural alternative to traditional antimalarial pharmaceuticals [62, 66]. In general, prior researches and other studies obviously shed light on the use of pomegranate, notably pomegranate peels, as an anti-malarial, and attributed this to the occurrence of the previously mentioned constituents. However, further studies are needed to determine the most effective dosage and administration of pomegranate for anti-malarial benefits, as well as to look into any potential adverse effects or interactions with other drugs. Moreover, human clinical trials are required to demonstrate the effectiveness of pomegranate as an anti-malarial drug.

5.5 Entamoeba histolytica

The protozoan parasite *E. histolytica* causes amoebic dysentery and liver abscesses. The disease is frequent in tropical areas where hygiene and sanitation are typically lacking. Other primates, in particular dogs, cats, and rodents, can all have amoebic dysentery. The other types of amoebae seen in feces are non-pathogenic; nonetheless, it is critical to accurately identify each kind to guarantee appropriate treatment, if necessary, and to avoid needless or improper therapy owing to misinterpretation [68, 69].

5.5.1 Antiamoebic activity of pomegranate

Pomegranate has been used as a traditional anti-diarrheal remedy since ancient times; in addition, modern science has confirmed this and attributed these properties to pomegranate due to the antispasmodic and antienteropooling properties pomegranate possesses, as well as tannin, which has antisecretory properties. Furthermore, a research conducted by Kritikar and Basu validated the efficacy of pomegranate in the treatment of diarrhea. Likewise, Das et al.'s investigation confirmed the therapeutic potential of pomegranate seed methanolic extract as an antidiarrheal pharmaceutical in rats [70, 71, 72]. Moreover, the rind of the fruit is beneficial for diarrhea and dysentery [9]. From the preceding, it is unambiguous that the pomegranate's anti-diarrheal activity has attracted the interest of researchers in studying its efficacy against amoeba infections, the most significant of which is *E. histolytica*. In one study, Segura and his colleagues discovered that tannins and alkaloid compounds extracted from pomegranate roots have anti-amoebic properties. In particular, the researchers noticed that only two milliliters of aqueous extract completely stopped the growth of this parasite. Moreover, the findings of their investigation revealed that alkaloids at a dosage of 1 mg/ml had no amoebicide activity, although tannins at a concentration of 10 µg/ml did. Furthermore, dry pomegranate peels have been used as an exceptional cure for dysentery and enteritis since ancient times [73, 74]. Pomegranate's antiprotozoal activity against *E. histolytica* was also demonstrated by Calzada et al. in their research. Their investigation illustrated the pomegranate's potential as a safe and effective natural treatment alternative for disease caused by *E. histolytica* [38]. While Dardona and Al-Hindi later studied the effect of alcoholic and aqueous extracts of pomegranate peels and pulp, as well as pomegranate juice, on *E. histolytica*; the results of their study revealed that the alcoholic extract of pomegranate pulp had the strongest anti-amoebic effect. Despite the fact that both the aqueous extract and the pomegranate juice were efficient anti-amoebic agents, in general, their research found that the alcoholic extract was more effective than the aqueous extract [75]. This implies that the bioactive ingredients

attributed to the anti-amoebic activity of pomegranate are more soluble in alcohol than in water. Further studies are required to determine and isolate these compounds for potential use as natural anti-amoebic agents.

5.6 Ascaris

The parasitic nematodes *Ascaris lumbricoides* and *Ascaris suum* are members of the *Ascarididae* family. Both of these parasites infect people and pigs. Furthermore, *A. lumbricoides*, the human roundworm, is one of the most frequent parasites in the world, infecting 1.2 billion individuals worldwide. *Ascariasis* is caused by the parasitic roundworm *A. lumbricoides* and is one of the most prevalent helminthes diseases globally, particularly in low-income countries. In children, the infection can cause malnutrition, stunted growth, and poor cognitive development, with a morbidity of roughly 10.5 million disability-adjusted life years (DALYs). Furthermore, 122 million occurrences of morbidity with major health implications are documented annually [76, 77]. *A. suum*, on the other hand, is a common parasitic worm that causes infection in pigs and has a high prevalence rate in host populations. Because of decreased productivity and increasing death rates, the parasite is responsible for enormous economic losses on the pig farms. To mitigate the hazards and manage *A. suum* infections in pig populations, control methods such as anthelmintic therapy and enhanced hygiene practices are required. In addition, the incidence of *A. suum* infection varies depending on geographical location and farm management approaches; however, merely a few swineherds are completely free of infection [78, 79].

5.6.1 Anti- Anthelmintic activity of Pomegranate against A. suum

Different parts of the pomegranate plant, including the fruit hulls and roots, have been shown to have antihelmintic characteristics. Several significant alkaloids, notably pelletierrines, have been identified and demonstrated to have anthelmintic activity. The most common use has been as a vermifugal or tanicidal agent (that is, a killer and expeller of intestinal worms). These alkaloids have long been used to treat parasitic ailments, and recent research has shown encouraging results in their usage against drug-resistant parasite strains [42, 80]. Despite its long history of usage in traditional medicine, this plant's antihelminthic effects have recently been thoroughly researched. Researchers discovered that the bioactive chemicals present in it, including tannins and alkaloids, had powerful antiparasitic properties. In fact, several studies have found that extracts of this plant are as effective as commercial antiparasitic medications in treating specific forms of intestinal worms. Furthermore, because it is a natural medicine, it may be safer and less expensive than conventional therapies [61]. Moreover, Amelia and her colleagues did a research *in vitro* to investigate the impact of pomegranate peel (*P. granatum L.*) as an anthelmintic on female *A. suum*. The effect of pomegranate peel extract on 900 female *A. suum* was studied. *A. suum* was distributed into groups, with the amount of pomegranate peel extract increasing from one to the next. The findings of their study revealed that the higher dose of pomegranate peel extract resulted in a higher percentage of dead worms, so that pomegranate peel extract at a concentration of 75% gave the highest worm-killing rate, reaching 82%, but its potential was less than that of mebendazole, which kills 100%. Significant differences in the treatment with pomegranate peel extract at various doses were observed ($p < 0.05$). Pomegranate peel extract provides anthelmintic activity against *A. suum* females *in vitro*, based on their study's findings [81].

5.7 Monogeneans Fish Parasite. *Dactylogyrus sp*.

The genus *Dactylogyru s*sp. is a monogenetic parasite that causes a disease called Dactylogyrus in fishes. Furthermore, *D. diffformis* is known to inflict significant damage to its host's gill tissue, resulting in difficulty breathing and lowered growth rates. Adults of these parasites have been found linked to the host's gill tissue through a distinctive structure with a row of hooks and sometimes suckers. According to Ozturk and Altunel (2006), the prevalence of *D. diffformis* infections was greater in younger fish than in older fish. Younger fish may have a higher frequency of diseases due to their weakened immune systems and susceptibility to parasite infestations [82, 83].

5.7.1 Antiparasitic Activity of Pomegranate against Dactylogyrus sp.

Van and colleagues conducted a research to assess the *in vitro* antiparasitic properties of pomegranate peel (*P. granatum*) against *Dactylogyrus* sp. In their investigation, parasites were exposed *in vitro* to varying amounts of pomegranate peel extract. At 3 minutes after exposure to pomegranate peel at a concentration of 500 mg/ml and at 6 minutes after exposure to 250 mg/ml and 100 mg/ml, cumulative mortality was determined to be 100%. 6 minutes after being exposed to pomegranate peel at a concentration of 50 mg/ml, the cumulative death rate was 66%. Pomegranate solutions demonstrated antiparasitic effects on *Dactylogyrus* sp. *in vitro*. To some extent, depending on the solution concentration and exposure period [84]. *In vivo* investigations should be implemented to prove the effectiveness of pomegranate peel solutions against Monogeneans in fish to assess the potential of pomegranate peel as a natural and safe alternative to synthetic medicines. These experiments will give significant details on the safety and efficacy of this fish farming strategy.

5.8 Cryptosporidium spp

Cryptosporidium is an intracellular, extra-cytoplasmic protozoan parasite with a monoxenous host that causes cryptosporidiosis. Furthermore, it belongs to the Apicomplexa with special characteristics such as the ability to initiate self-infections, an unusual location within the host cell, and innate resistance to disinfectants. Two organisms, *C. hominis* and *C. parvum* cause 90% of human infections. Cryptosporidiosis symptoms include dehydration, stomach discomfort, and diarrhea. Additionally, cryptosporidiosis is a disease that is disseminated by contaminated water sources such as swimming pools and drinking water. Proper hygiene habits and clean drinking water sources are among the prevention methods [85].

5.8.1 Cryptosporicidal activity of pomegranate

Al-Mathal and Alsalem (2012) performed a significant investigation examining the impact of pomegranate peels on neonatal *Albino mice* infected by oral injection of *C. parvum* oocysts in order to investigate the antiparasitic activity of pomegranate against *C. parvum*. The treated mice received oral administration of aqueous solutions of *P. granatum* peel (3 mg/kg body weight) after inoculation. Improvement was seen when variables such as diarrhea, oocyst shedding, weight gain or loss, and the histology of ileal sections were examined. *P. granatum* peel solution treatment of infected mice resulted in continuous weight increase, better intestinal histology, full elimination of oocyst shedding, and substantial reductions in *C. parvum* trophozoites and lymphatic infiltration [86, 87]. These findings suggest that *P. granatum* peels are a safe and efficient therapy for *C. parvum*-induced cryptosporidiosis. This result is significant since cryptosporidiosis is a major cause of diarrhea in children across the world and because the available treatments are ineffective and have negative side effects. Peels of *P. granatum* may thus be a potential alternative therapy for this infection.

5.9 Eimeria

Apicomplexan parasites that invade the intestines, causing coccidiosis, a serious intestinal disease with global economic implications. The ailment has significant morbidity and mortality rates, with symptoms ranging from severe hemorrhagic enteritis to asymptomatic disease. However, the occurrence of intestinal lesions is dependent on the species of *Eimeria*. *Eimeria tenella, Eimeria necatrix, Eimeria acervulina, Eimeria maxima, Eimeria brunetti, Eimeria mitis, and Eimeria praecox* are the most significant species. These *Eimeria* species are responsible for coccidiosis in chickens, which is a serious threat for the global poultry industry. Proper management methods and prompt treatment can aid in disease prevention and control [88].

5.9.1 The activity of pomegranate against Eimeria

Khorrami and colleagues investigated the effect of pomegranate peel extract on *Eimeria* in order to assess the antiparasitic activity of pomegranate. They conducted experiments on 300 broiler chicks and divided them into groups so that they were infected with common *Eimeria*, and when infection occurred and symptoms appeared on the infected chicken, the researchers gave the chicken pomegranate peel extract for 7 days, and the chicken was euthanized at the age of 35 days. Simultaneously, all intestines and liver were kept in 10% formalin for tissue investigation, and growth indicators were recorded and checked weekly at all phases of growth. The results showed that adding pomegranate peel extract, particularly at 400 ppm, could reduce intestinal lesions and oocytes per gram, but at this dose, growth indices can be negatively influenced, whereas administration of toltrazuril had the best effect on oocytes per gram and intestinal lesions but had no effect on growth indices in challenged chickens. Furthermore, supplementation with 400 ppm pomegranate peel extract can cause liver damage, but the lower amount had no impact on liver tissue. Their research also concluded that it is required to identify beneficial ingredients in pomegranate peel extract and to prepare serial dilutions in order to get the ideal dose with the best anti-coccidial activity and the least detrimental effect on growth indices in chickens [89]. Poultry farming is a significant sector that demands careful consideration of the products needed to keep the birds healthy. Pomegranate peel extract has been recognized as a possible anti-coccidial agent; nevertheless, its dose and any adverse effects must be meticulously considered prior to usage. To guarantee safe and successful use, it is critical to understand the active ingredients in pomegranate peel extract and their ideal concentrations. Future research can concentrate on identifying these chemicals and their impact on poultry health, as well as discovering the most effective means for administering the extract.

5.10 Leishmania

Leishmaniasis is a parasitic disease disseminated by the bite of infected sand flies and caused by numerous species of the genus *Leishmania* known as hemoflagellates. The disease's symptoms fluctuate between mild and severe; furthermore, they can affect the skin, mucous membranes, and internal organs. It is common in arid environments. Furthermore, the disease may be found in both the old and new worlds (the Americas). The parasites infect and grow

in macrophages after infection, as well as being captured by sand flies when they feed on the blood of an infected human. Kala-azar, or old-world visceral leishmaniasis, is a potentially lethal disease that affects the liver, bone marrow, and lymph nodes. It is prevalent in Africa, Asia, and South America. *L. donovani, L. chagasi*, or *L. infantum* can cause the visceral form [90].

5.10.1 Leishmanicidal activity of pomegranate

In a recent study conducted in 2019, the antiparasitic activity of pomegranate peel extract against *Leishmania* was assessed. *L. infantum* promastigotes were treated with pomegranate (*P. granatum*) peel extract (PPE) to test its antiparasitic effects. The extract, which was evaluated by NMR and HPLC analysis, suppressed parasite growth in a dose-dependent manner, as demonstrated by the MTT experiment. Furthermore, the reversibility experiment revealed that PPE had apoptosis-mediated leishmanicidal activity, which was validated by DNA fragmentation and real-time PCR studies. Consequently, morphological and ultra structural modifications generated by a *P. granatum* extract on *Leishmania* were shown for the first time using light, transmission, and scanning electron microscopy. These results point to PPE as a possible leishmaniasis therapy alternative, particularly in areas where other options are scarce or inadequate. For PPE to be evaluated for effectiveness and safety *in vivo*, more research is required [91]. It is noteworthy that the antiparasitic activity of pomegranate against *Leishmania* was not limited to pomegranate peels; pomegranate juice has additionally demonstrated efficacy against cutaneous leishmaniasis. Pomegranate juice's leishmanicidal effect is mainly caused by its anti-inflammatory and antioxidant properties [92]. In conclusion, cutaneous leishmaniasis is an ailment caused by a parasite that affects millions of individuals worldwide. Traditional treatments for this ailment can be expensive and have severe side effects, making them difficult for some patients to tolerate. Nevertheless, pomegranate juice may be a natural and cost-effective alternative therapy. Patients who use pomegranate juice as a natural therapy for cutaneous leishmaniasis may avoid the harmful side effects of standard medicines while simultaneously benefiting from its possible therapeutic abilities.

5.11 Other parasites

Pomegranate's anti-parasitic impact was not restricted to the aforementioned parasites; thus, the researches were expanded to cover numerous parasites that infect animals and humans. El-Sherbini and colleagues, for instance, investigated the antiparasitic activity of pomegranate against *Trichomonas vaginalis*. *In, in vitro* and clinical research, pomegranate juice was given to patients with *T. vaginalis* infections, and the symptoms went away after two months. The *in vitro* study found that pomegranate juice had a substantial influence on the growth of *T. vaginalis*, correlating with the clinical trial results [93]. Additionally, pomegranate alkaloids in the root, tree bark, and, to a lesser extent, fruit rind help the "tapeworm" to loosen its grip on the gut wall, allowing the weaker parasites to be easily evacuated by a second herbal treatment, a cathartic one [14, 28]. Intriguingly, research on pomegranate's antiparasitic effectiveness has expanded to encompass veterinary parasites. Dos Anjos and colleagues, for instance, investigated the use of an aqueous extract of pomegranate stem bark, particularly the dried extract, which demonstrated effectiveness *in vitro* in their research. According to the findings, pomegranate stem bark extract may be a potential alternative to traditional anthelmintic medications in the management of bovine worms [94]. In addition, pomegranate peel extract has the potential to be employed as an alternate therapy for blastocystosis and in the development of innovative anti-Blastocystis medicines. Besides, these findings provided clinical proof that pomegranate peel extract contains components that serve as potent antioxidants [95].This shows that pomegranate peel extract has the potential to cure additional parasitic ailments as well as serve as a natural source of antioxidants for overall health improvement. Eventually, a research observed that *P. granatum* might be used to treat parasitic nematodes in ruminant animals. Numerous studies have also demonstrated that pomegranate components aid in the treatment of worm infections. Given this likelihood, this effort should be expanded to isolate, separate, identify, and describe the components responsible for this plant's anthelmintic abilities [96]. Additional investigation is needed to determine the effectiveness of *P. granatum* versus parasitic nematodes *in vivo*. This might aid in the creation of a natural and effective anthelmintic medication for the treatment of parasitic nematodes in humans as well as animals. Such a medicine may have fewer side effects and be less expensive than currently available synthetic pharmaceuticals.

5 Conclusion and Recommendations

The current investigation concluded after a review of several related studies, researches, and publications that the pomegranate has been of tremendous relevance since ancient times, both medically and nutritionally, considering that it contains numerous vital compounds. This review study also revealed that pomegranate has undeniable anti-parasitic properties, though future research in this field should broaden the types of parasites tested as well as conduct more research *in vivo* and isolate its significant active chemical components. In addition to identifying optimum dosages for humans in order to achieve safe, effective, and natural remedies from pomegranate without side effects, as well as to avoid parasite and microbe resistance to manufactured medicines and antibiotics in general, the study additionally

revealed that pomegranate might assist in curing disorders including diabetes, cardiovascular disease, and other ailments. Pomegranate is plentiful in antioxidants, which protect the body from oxidative stress, which is a primary cause of chronic diseases. Furthermore, it has been realized that pomegranate improves brain function and memory, making it a promising natural treatment for neurodegenerative diseases. Overall, the advantages of pomegranate are copious, and further studies are required to completely comprehend its therapeutic characteristics and prospective applications in modern medicine.

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