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Review Article

Present and Future Potential of Antiparasitic Activity of *Opuntia ficus-indica*

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ABSTRACT

The prickly pear, *Opuntia ficus-indica* of the Cactaceae family is important in agricultural economies throughout arid and semi-arid regions. It has multiple uses in folk medicine of different countries since ancient times. This makes it a promising multi-purpose plant for use as food, therapy, and other purposes. Treatment with medicinal and aromatic plants and the use of their biologically active products, especially as anti-parasites, has become a very important and urgent matter due to the need for new anti-parasite drugs, as a result ofthe emergence of some strains of parasites resistant to chemotherapy. The present review highlights the importance of *Opuntia ficus-indica* as antiparasitic agentand the possibility of using*Opuntia ficus-indica* as the most valuable and promising plant in the pharmaceutical industry to treat diseases caused by infection with parasites.

Keywords: *Opuntia ficus indica*, Antiparasites, Plant active components, Phytotherapy.

Introduction

One of the most important plant that has received greatattention in recent years, especially in arid and semi-arid areas, is prickly pear cactus (*Opuntia ficus indica*) due to its tolerance of drought, high temperatures and poor soils. *Opuntia ficus-indica* is a bushy or erect and tree-like perennial succulent with a definite woody trunk, with a large top.[1] It is characterized by being fast growing and its edible fruits are harvested 3 years after planting .[1] Fruits are ovoid to oblong with sometimes spines, normally red to purplish, green, yellow or orange, fleshy, juicy, edible, able to storage for several months. The pulp may be white-yellowish, orangish or purple-red.

It is native to Mexico, but now cultivates in the rural areas of the many countries, where plants play an important role in the economic life of rural residents as a source of food for humans (consuming both the fruits and pad), beverages, and livestock fodder, soap, drinking water purification and as a protective hedge for fencing,[2,3] also dye as host plants for the cochineal insect (*Dactylopius coccus*). Cochineals are used to make carmine dye, a highly prized red dye for textiles.[4]

Historically, the prickly pear has been used in traditional medicine to treat digestive problems, anemia, ulcers, bronchitis, edema, urinary problems, fever, inflammation, vitiligo, and for burn and wound care. Also, it has been used as a diuretic, treatment of liver problems, hemorrhoids, bladder stones, inflammation of the eyes, lower back pain, spleen enlargement, and management of human immunodeficiency virus (HIV) and tumors.[2,3,5] Among the traditional uses of pads/cladodes are to relieve heat and inflammation, and wound care., while flowers are used for treatment of lung problems, including bronchitis and asthma, and also fruits are used to treat gonorrhea and Whooping cough, expel phlegmfrom the lungs, control excessive coughing, and increase bile secretion. Also, a treatment for diabetes, prostate enlargement and rabies.[6]

There are many varieties /cultivars of cactus pear that contain a variety of nutrients, vitamins, minerals and bioactive compounds in both pad (cladode) and fruit that are beneficial for human health. Among the important nutritional and health-promoting benefits that attracted the researchers' attention was the fact that the cactus pear fruit is rich in bioactive antioxidant compounds including ascorbic acid and polyphenols and betalains.[7] Antioxidant pigments betalains according to the colour of the fruit including betacyanins in the purple variety and betaxanthins in the orange variety,[8,9] which are important in reducing low-density lipoprotein cholesterol levels after consumption and protect against oxidation.[10] Also, numerous flavonol glycosides, plant-derived secondary metabolites with important antioxidant properties, have been isolated from *O. ficus-indica* fruits.[11]*O. ficus-indica* pads/cladodes contain manganese, which is essential for glucose metabolism,[12,13] and helps the body regulate protein synthesis, muscle and nerve function, blood glucose, and blood pressure. Many studies reported the chemical composition of the fruits and cladodes of the prickly pear and their nutritional components such as crude fiber, vitamin C, calcium, magnesium, potassium, phosphorus, iron, sodium, betanin and *β*-carotene, in addition to their use as a source of many pharmaceutical products.[1,14]

Pharmacological studies have found the health benefits and curative effects of the *Opuntia ficus-indica* as anti-diabetic,[15,16] antihypercholesterolemic and anti-hyperlipidemic,[17] anti-stress,[18] anti-uric and diuretic, anti-inflammatory,[19] anti-cancer,[20] gastritis, arteriosclerosis, prostate hypertrophy,[21] antioxidant, antimicrobial and neuroprotective properties.[22]

Recently, the interest in plants bioactive compounds has increased as alternatives to chemical medicines due to the emergence of some strains of parasites resistant to available medicines.[23]This was evident from the expansion in the use of plant extracts in human and veterinary medicine as an aid or alternatives to the prevention and treatment of diseases, caused by parasites.[24]

Plants with beneficial properties are known in traditional medicine. Nowadays, in spite of the widespread availability of synthetic compounds, research still focus on natural compounds due to their

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lower cost and fewer side effects. The increasing interest in preventive medicine encourages use of nutraceuticals, bioactive compounds of vegetable origin with important nutritional values. Among the medicinal plants, *Opuntia ficus-indica* is widely known for its beneficial properties.The aim of the present review is to stress the major classes of *Opuntia* components and their medical interest through emphasis on some of their biological effects, particularly those having antiparasitic effects.

Globally, parasites attract wide attention, being one of the most important causes of disease and death. Parasites are generally transmitted through water, blood, food-and vector.[25] We will focus this review on the fact that *Opuntia ficus-indica* is a new source that could be used as a treatment alternative due to its content of numerous anti-parasite compounds.[26,27] So, this review lists the studies that have efficiently and effectively cited prickly pears as a source of active agents as anti-parasites for the following parasites;*Leishmania* spp; malaria and roundworms.

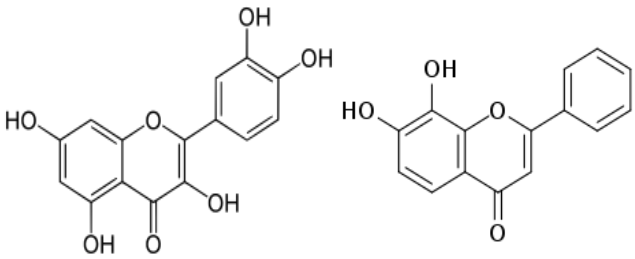
Antileishmanial property of Opuntia ficus-indica

Leishmaniasis is one of the most neglected tropical infectious diseases in the world caused by protozoan parasites from more than 20 *Leishmania* species. These parasites are transmitted to humans by the bite of an infected female phlebotomine sand-fly insect vector. Over 90 sand-fly species are known to transmit Leishmania parasites. There are three main forms of the disease: cutaneous leishmaniasis, visceral leishmaniasis (kala-azar), and mucocutaneous leishmaniasis. cutaneous leishmaniasis is the most common form, while visceral leishmaniasis is the most severe form and mucocutaneous leishmaniasis is the most disabling form of the disease.[28] Statistics has shown that 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. Leishmaniasis disease is associated with malnutrition and a weak immune system.[28]

Visceral leishmaniasis is also known as kala-azar is fatal if left untreated in over 95% of cases. It is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anemia. An estimated 50 000 to 90 000 new cases occur worldwide annually. It remains one of the top parasitic diseases with outbreak and mortality potential. The most cases reported to WHO occurred in Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan. Cutaneous leishmaniasis is the most common form of leishmaniasis and causes skin lesions, mainly ulcers, on exposed parts of the body, leaving life-long scars and serious disability or stigma. Most cases occur in the Americas, the Mediterranean Basin, the Middle East and Central Asia. According to WHO reports, the most cases occurred in Afghanistan, Algeria, Bolivia, Brazil, Colombia, Iran, Iraq, Pakistan, the Syrian Arab Republic and Tunisia. It is estimated that between 600000 to 1 million new cases occur worldwide annually. Mucocutaneous leishmaniasis leads to the partial or total destruction of mucous membranes of the nose, mouth and throat. The most cases reported to WHO occurred in Bolivia, Brazil, Ethiopia and Peru.[28]

Parasite drug resistance is a challenge to our efforts to control the leishmaniases. Several factors have contributed to the diminished efficacy of chemotherapy registered for use against these diseases, including changes in host immunity associated with the global HIV/AIDS epidemic. Emergence of drug resistance and toxicity and the high cost of the available drugs with a lack of new anti-leishmanial drugs highlight the need to search for alternatives which is represented in plants and testing of plant compounds as antileishmanial activities.[29-31] as well as the urgent need to adopt strategies to monitor planttherapy efficacy to enable further research and continue efforts to control the leishmaniases as a global health problem.[29]

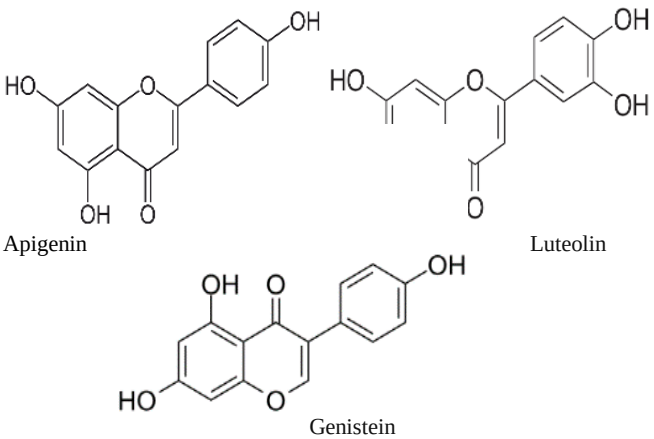
In this regard and unfortunately, one study was carried out on the *Opuntia ficus indica* to test its ability against Leishmania spp. The results showed that *Opuntia ficus indica* cladodes/fruits ectract exhibited an activity against *Leishmania major* and *Leishmania donovani* as well as a poor activity against *Trypanosoma brucei*.[32]The study concluded that caffeic acid and α-sitosterol have anti-leishmanial and anti-trypanosomal activities. A study carried out in Algeria, 2017 concluded that caffeic acid and quercetin have leishmanicidal effect and both are a potential therapeutic role against cutaneous leishmaniasis.[33]They showed that caffeic acid and quercetin induced necrosis and apoptosis. However, quercetin inhibited the growth of both promastigotes and amastigotes of *Leishmania donovani* by the blockade of DNA synthesis, and caffeic acid has a strong leishmanicidal activity on *Leishmania major* amastigotes buried in macrophages.[34-36] Apoptosis inducing factor can contribute to caspases independent cell death by affecting mitochondrial function and inducing chromatin degradation.[37] Other studies observed the immuno-modulatory effects and ant-ileishmanial activity of polyphenols; phenolic acids (caffeic acid), flavonoids (quercetin), and tannins.[34-36] However, *Opuntai ficus indica* has biological potential and plays an important role as a source of natural phenolic compounds.[38,39]The effect of *Opuntia ficus indica* as anti-leishmanial against *Leishmania braziliensis*, *Leishmania infantum* and also *Trypanosoma cruziis* due to the phenolic compounds.[40] This result was confirmed by another study that phenolic compounds; quercetin and its derivatives (7,8-dihydroxyflavone) (Figure 1) have potent and efficient antiparasitic activity against *Leishmania donovani*, with IC_{50} of 1.0 lg/mL, and with less effect against *Trypanosoma cruzi*.[41] Moreover, flavonoids have been shown to induce apoptosis of host cells[42] or by directly inducing apoptosis of the parasite[42,43] and quercetin directly promoted *Trypanosoma brucei* death by apoptosis.[43]



Quercetin 7,8dihydroxyflavone

Figure 1: Chemical structures of Quercetin and its derivatives (7,8-dihydroxyflavone)

Quercetin and other flavonoids are highly effective against *Cryptosporidium parvum* and *Encephalitozoon intestinalis*.[44,45] Quercetin inhibit DNA topoisomerases, promoting site-specific DNA cleavage resulting in the growth inhibition of *Leishmania donovani* promastigotes and amastigotes.[42] In *Toxoplasma gondii*, quercetin suppresses bradyzoite development *in vitro* through its ability to inhibit the synthesis of Hsp90, Hsp70, and Hsp27, factors that protect virulent parasites from the effects of host immune responses.[46] Other flavonoids, such as apigenin and genistein (Figure 2) are protein tyrosine kinase inhibitors and inhibit *Toxoplasma gondii*[47] and *Cryptosporidium parvum*.[48] Additionally, luteolin is an effective antileishmanial agent.[42]



Apigenin Luteolin

Genistein

Figure 2: Chemical structures of some flavonoids with Antileishmanial activity

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Antimalarial activity of Opuntia ficus indica

Malaria is a life-threatening disease and still considered as a major global health problem, caused by parasites that are transmitted to people through the bites of infected female Anophelesmosquitoes. Statistics for 2018 indicate 228 million cases of malaria worldwide, and 405000 deaths. However, children aged under 5 years are the most vulnerable group affected by malaria; about 272000 deaths worldwide, where, more than 90% of cases and deaths are in the African region.[49]

Malaria is caused by plasmodium parasites and transmitted to the human through the bites of infected female Anopheles mosquitoes. Five parasite species cause malaria in humans, and 2 of these species – *P. falciparum* and *P. vivax* pose the greatest threat. *P. falciparum* accounted for 99.7% of estimated malaria cases in the WHO African Region, 50% of cases in the WHO South-East Asia Region, 71% of cases in the Eastern Mediterranean and 65% in the Western Pacific. Whereas, *P. vivax* is the predominant parasite in the WHO Region of the Americas, representing 75% of malaria cases.[49]

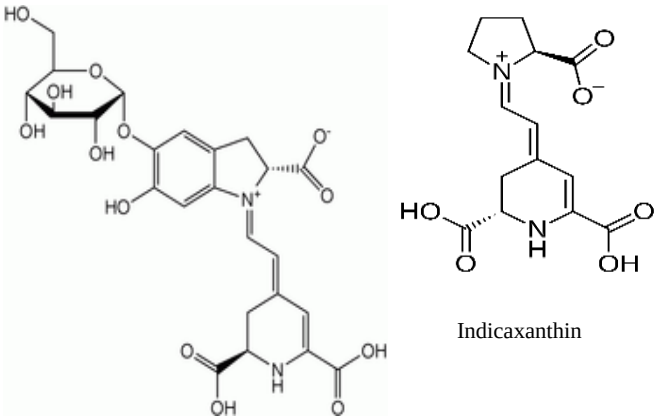
Resistance to antimalarial medicines is a recurring problem. The resistance of *P. falciparum* malaria parasites to previous generations of medicines, undermine malaria control efforts.[49] Hence, the need for new antimalarial drugs. Previous findings of antimalarial agents such as quinine and artemisinin extracted from medicinal plants have also enhanced the possibility of discovering new antimalarial drugs from plant source.[50]The search for new antimalarial agents must continue at an unabated pace to meet the challenges posed by the antimalarial drug resistance. Plant secondary metabolites continue to play an important role in pre-clinical antimalarial drug discovery.[51]

In this regard, it was found from the study that was conducted*in vitro* and *in vivo* that, *Opuntia ficus-indica* fruits/cladodeso has antiplasmodial effects and it has a useful role for the development of antimalarial drug.[52] Moreover, the study attributed antiplasmodial activity of *Opuntia ficus-indica* to thehigh presence of flavonoids. So, the presence of flavonoids and other bioactive constituents is believed to have contributed to the observed antiplasmodial activity of *Opuntia ficus-indica*.[52] Also, the high content of phenolic compounds are responsible for antioxidant properties and anti-inflammatory activity,[53] and more, prickly-pear cactus also effectively inhibited cell growth in several different immortalized and cancer cell cultures *in vitro* and suppressed tumor growth in a nude mouse of ovarian cancer model.[54] and was observed that phenolic, flavonoids and polysaccharide contents in the methanol extract of spineless cactus(*Opuntia ficus indica*f. inermis) flowers and roots, reduced radical scavenging activity and the antiulcerogenic activity.[55-57]

From the foregoing we can conclude that natural products are considered as a key source for the discovery and development of therapeutic agents, especially after the discovery of some plants that showed anti-malarial activity.[51] And as a continuation of this effort, *Opuntia ficus-indica* has been tested as an antimalarial, and the results have proven the potential efficiency of cladodes extract in *in vitro*and *in vivo* anti-plasmodial activity against*Plasmodium berghei*.[52] Therefore, more study is needed to develop antimalarial agent from*Opuntia ficus-indica*. From the results of Gengatharan study,[58] it was found that betalains (Figure 3) are important for human health due to their biological and pharmacological properties such as antioxidant, anticancer, anti-lipidemic, antimicrobial. In addition, betalains showed capacity as antimalarial agent. This is due to its ability to chelate the indispensable inner cations (Ca^{2+}, Fe^{2+} and Mg^{2+}) in the parasite and block the parasites choline intracellular transport which is crucial for malarial parasite growth.[59]

From the results of previous studies, it was found that flavonoids including acacetin, baicaclein, chrysin, genistein, hesperetin, isoquercetin, kaempferol, luteolin, myricetin, naringenin and quercetin, have antimalarial activity and it was reported that flavonoids act by inhibiting the fatty acid biosynthesis in the parasite biochemistry. They also act probably by inhibiting the influx of L-glutamine and myoinositol into infected erythrocytes during intraerytrhocytic phase of *Plasmodium* life cycle.[60-62]

On the other hand, antimalarial activity of flavonoids occur by targeting certain functional biomolecules (protein, enzymes, DNA,etc.) that are essential for the parasite survival. The phenolic – OH groups of such polyphenolic flavonoids (hydroquinones) is readily converted to a stable phenoxy radical anion (semiquinones) under cellular oxidative stress (*in vivo*) which in turn exerts either oxidative damage to cellular components of parasites or direct tissue damage by irreversible covalent interaction with parasitic structural proteins or DNA. So, the antioxidant property of flavonoids is the basis of their antimalarial action.[63,64]



Betanin

Indicaxanthin

Figure 3: Chemical structures of some betalains

Other studies have proven the effectiveness of sesquiterpenes compounds in *Cyperus rotundus* (patchoulenone, *α*-caryophyllene oxide, 10,12-peroxycalamenene and 4,7-dimethyl-1-tetralone) and their anti-malarial activity.[65,66] The same approach was found from a recent study that reported the *Cyperus articulatus* essential oil has anti-malarial (*Plasmodium falciparum*) due to the compounds; mustakone, cyclocolorenone, cyperotundone, α-cyperone, α,β-unsaturated carbonyl moiety.[67] This is likely to be due to the antimalarial potential of these compounds which may be related to the tendency of the nucleic acids of *Plasmodium* to react with the α,β-unsaturated carbonyl moiety.[68]

With regard to volatile oil, the components of the oil extracted from *Opuntia ficus indica* were identified as follows, unsaturated fatty acids, triacylglycerols, phytosterols, and tocopherols.[69] Also, the antimicrobial efficiency of *Opuntia ficus indica* oil is due to its richness in phytosterols, especially beta-sitosterol, which act by inhibiting microbial growth, and also by interfering with the cell membrane sterols, and thereby altering its permeability to nutrients, which may result in the disruption of the cell vital pathways and so induce necrosis of pathogenic cells.[70,71] All these active molecules could act separately or in synergy to enhance their effectiveness. The oil also has proven biological efficacy as antimicrobial agent against bacteria, yeasts and fungi.[72]Fatty acids like linoleic and oleic acids have antibacterial activity.[73] This is a result of its role in inhibiting membrane enzymatic activities such as glucosyltransferase and on the other hand by activating autolytic enzymes in the pathogen cell wall and this leads to a disorganization of the membrane phospholipids bilayer, which may result in a notable decrease in nutrient uptake, the inhibition of bacterial cell growth, and an increase in membrane permeability and cell lysis.[74]

The fatty acids found in *Opuntia ficus indica* seed oil are linoleic acid as the major fatty acid (61.01%), followed by oleic (25.52%) and palmitic (12.23%) acids. Both myristic, stearic and arachidonic acids were detected in low amounts. As a result, *O. ficus indica* seeds are an important source of natural fiber and, given its high linoleic acid content, its oil can be used as a nutraceutic agent.[75] In another study, linoleic acid (22.3%), palmitic acid (12.7%), lauric acid (10.5%) and myristic acid (4.2%) were major fatty acids of *O. ficus-indica*.[76]Moreover, the essential oils composition of the skin, pulp and

seeds from the fruits of *Opuntia ficus-indica* have antioxidant, and antimicrobial activities.[77]

Effect of Opuntia ficus indica on parasitic nematodes

Parasitic nematodes (roundworms) of small ruminants and other livestock are major concern and also have major economic impacts,[78] because it causes diseases of major socio-economic importance worldwide, the annual cost associated with parasitic diseases in sheep and cattle has been estimated at 1-10 billion US dollars worldwide.[78] Parasitic nematodes of livestock are controlled mainly through anthelmintic treatment, this type of control is expensive andineffective in some cases. Besides, the excessive and frequent use of anthelmintics has resulted in substantial and widespread problems with anthelminthic resistance in nematode populations.[78-80] For this reason, there is a need to focus on planttherapy, and studies have intensified and experiments developed to produce medicines from *O. ficus-indica* for their efficacy in controlling parasitic nematodes has been proven.[24,27]

Phenolic compounds include many compounds such as phenols, phenolic acids (derivatives of benzoic and cinnamic acids), coumarins, stilbenes, condensed, and hydrolysed tannins, lignins, and majorly flavonoids (including flavonols, flavones, flavanones, flavanols or catechins, anthocyanins, isoflavones, chalcones and dihydrochalcones) are found in many plants.[81,82] Quercetin (3,3,4,5,7-pentahydroxyflavone) a flavonol are important due to its biological activities as antioxidant, anti-inflammatory and antiparasitic agents,and for its health benefits associated with the prevention and therapy of cardiovascular diseases and cancer.[83]

Tannins(Figure 4) on the other hand possess anthelmintic properties.[84-87] This was confirmed by Williams[88] in his study of the effectiveness of tannins against*Ascaris suum*.

Multiple studies have been conducted on the biological importance of tannins as an antimicrobial,[89] anti-fungal (*Candida albicans*),[90] Anti-trypanosoma (*Trypanosoma brucei*),[91] and anti-leishmanial agent (*Leishmania donovani*).[92] In addition, a number of studies reported that tannin-containing plants have anthelmintic effects.[93] Furthermore, tannins have been shown to have efficacy against hookworm and pinworm,[94,95] and are speculated to be responsible for the anthelmintic effects against *Ascaris* and other livestock parasites such as *Haemonchus contortus*.[96-98]

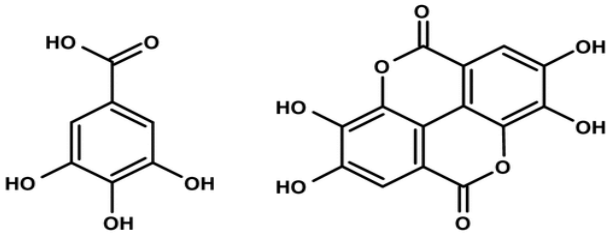


Figure 4: Types of tannins and their basic structures; (a) hydrolysable and (b) condensed

The natural anti-parasite effect of *Opuntia ficus indica* may be due to the presence of phenolic compounds, and more specifically the quercetin derivative and probably from the tannin-rich components which have a higher efficacy against gastrointestinal nematodes of sheep.[24,99] The antiparasitic activity is as a result of the synergistic effects among compounds, such as quercetin derivatives.[85,86] Tannin-rich plants have been used against gastrointestinal parasites by promoting structural alterations in the parasites, reducing the development of the larval stages and compromising the fertility of females and egg integrity (hatchability).[99-101]

The anthelminthic activity of the cactus pear is attributed to the sum of the effects of phytochemicals such as saponins flavonoids, plant pigments, and tannins.[27]*Opuntia-ficus indica* cladodes is considered as a suitable ecofriendly product that could control gastrointestinal parasites of sheep. So, *Opuntia-ficus indica* cladodes extract is a promising therapeutic alternative.[102]

Previous studies attributed the biological activity of *Opuntia ficus-indica* to its high content of many bioactive compounds, such as betalains, polyphenols, terpenoids, vitamin C, minerals, proline, taurine,[103-107]and also isorhamnetin glycosides, especially isorhamnetin-3-O-rutinoside and isorhamnetin triglycosides.[38]Recent experiments have found that*Opuntia ficus-indica* fruits is a unique source of quercetin,terpenoids, tannins, other phenolics and flavonoidswhich may predominantly be responsible for the biological effects of *Opuntia ficus-indica*, such as its antimicrobial, antioxidant and anthelmintic activities.[107-114]

Conclusion

A wide array of parasites infects humans and animals, causing some of the most prevalent infectious diseases globally. Recent advances in the treatment of malaria, leishmaniasis, and Helminth infections are managed with pharmaceutical alternatives, despite a relatively narrow therapeutic pipeline for new antiparasitic drugs; there have been significant improvements in the treatment of these widespread infections in the past two decades. There is an urgent need for serious research into the use of plant remedies as anti-parasitic agents, and to overcome parasite resistance to chemical drugs.*O. ficus indica* plant may be useful in the future in the discovery of anti-parasitic plant compounds. Therefore, there should be an increased focus on the chemistry of prickly pears, and test these compounds for their anti-parasitic activity.

Conflict of interest

The authors declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this manuscript is original and that any liability for claims relating to the content of this manuscript will be borne by them.

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