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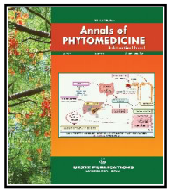

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A review on kala-azar and management with Ayurveda herbs

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Abstract

Leishmaniasis is a neglected public health problem that largely affects the impoverished people of developing nations. It is caused by protozoan species that are members of the genus Leishmania. The causative organism is dispersed by female sandflies. Visceral, mucocutaneous, and cutaneous symptoms are the most prevalent clinical manifestations of leishmaniasis. Miltefosine, amphotericin B, and pentavalent antimonials are only a few of the drugs that are used to treat this significant infectious condition. Apart from that, these medications have very bad side effects in humans, and the exorbitant price of liposomal amphotericin B prevents them from being used in low-income nations. Moreover, certain parasite species have developed medication resistance. The scarcity of drugs and the side effects of currently used drugs, it is necessary to find novel medications with leishmanicidal activity. Although, the term "kala-azar" is not used in Ayurveda; it describes three diseases, visamajvara (a type of fever), plihodara/pliharoga (splenomegaly), and raktaja krimi (microorganism in blood), which are similar to Indian kala-azar and appear to be appropriately correlated based on their etiology, prognosis, symptomatology, and treatment. Kala-azar can be effectively treated with ayurvedic herbs like Guduci (*Tinospora cordifolia*), Katuki (*Picrorhiza kurroa*), Daruharidra (*Berberis aristata*), Kumari (*Aloe barbadensis*), and Earanda (*Ricinus communis*), *etc*. An emphasis on medicinal herbs used to treat leishmaniasis is particularly apparent in this review. New antileishmanial drugs can be discovered and produced using the bioactive phytochemicals found in plants.

1. Introduction

The disease leishmaniasis is spread through the bite of specific sandfly species (subfamily Phlebotominae), which are infected by protozoan parasites of the genus Leishmania (Kharaji *et al.*, 2016). Other names for leishmaniasis are: kala-azar, Delhi boil, Oriental sore, and espundia. Depending on the organ system it affects, leishmaniasis can be classified into several kinds, including viscerotropic leishmaniasis, post-kala-azar dermal leishmaniasis, mucocutaneous leishmaniasis, cutaneous leishmaniasis, and visceral leishmaniasis (Bifeld and Clos, 2015). The World Health Organisation estimates that there are between 600, 00 and one million new cases of cutaneous leishmaniasis and between 50,000 and 90,000 new cases of visceral leishmaniasis per year (WHO, 2020). Environmental factors including deforestation, irrigation projects, dam construction, and urbanization have been linked to the rise in cases in recent decades. Miltefosine, amphotericin B, and pentavalent antimonial are only a few of the drugs that are used to treat this significant infectious condition. Apart from that, these medications have very bad side effects in humans, and the exorbitant price of liposomal amphotericin B prevents them from being used in low-income nations. Moreover, certain parasite species have developed medication resistance. The scarcity of drugs and the side effects of currently used drugs, it is necessary to find novel medications with leishmanicidal activity (Charlton *et al.*, 2018).

Medicinal plants are thought to be a significant source of novel compounds with possible medical use (Ramakrishna *et al.*, 2023; Nadeem *et al.*, 2022). There was antileishmanial activity observed in several natural products, such as naphthoquinones, neolignans, lignans, alkaloids, chalcones, and triterpenoids. India is blessed with an incredible abundance of medicinal plants and a deep understanding of their traditional use in the ayurvedic medical system. This country has earned the moniker “Medical Garden of the World” due to its tremendous biodiversity (Li *et al.*, 2020). This review therefore aims to explore knowledge regarding medicinal plants mentioned by traditional medicine that are used to cure leishmaniasis.

2. Review on kala-azar

The protozoa in the genus Leishmania infect humans and animals to produce leishmaniasis. Leishmaniasis is caused by at least 23 species of Leishmania. The disease can take three forms; mucocutaneous (mucous membranes), which is extremely uncommon; cutaneous (skin), which is the most common form; and visceral (internal organs). Generally speaking, various Leishmania species induce varied manifestations of the illness. Other names for leishmaniasis are kala-azar, Delhi boil, and oriental sore. Phlebotomine sandfly, a microscopic insect vector that is between two and three millimetres long, is responsible for leishmaniases. Only around 30 of the 500 known species of phlebotomine have been conclusively identified as

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the disease's carriers. The protozoa are only spread by the female sandfly, which also infects itself with Leishmania parasites found in the blood it suckers from its human or mammalian host to get the protein needed to grow eggs (Sharmila, 2013).

Certain types of the disease may spread between humans, but the majority is exclusively contagious through animals (zoonosis). Twenty-one of the thirty species that infect mammals are responsible for human infections. These include the three species in the *Leishmania donovani* complex (*L. donovani*, *L. chagasi*, and *L. infantum*); the three main species in the *Leishmania mexicana* complex (*L. mexicana, L. venezuelensis*, and *L. amazonensis*), and the four main species in the subgenus *Viannia* (*V. guyanensis*, *V. braziliensis*, *V. peruviana,* and *V. panamensis*). Although, there is no physical difference between the various species; they can be distinguished using isoenzyme analysis, DNA sequence analysis, or monoclonal antibodies (Meena *et al*., 2010).

2.1 Transmission

Through feeding on a reservoir host, the healthy sandfly acquires the infection. Leishmania is spread through the bite of female phlebotomine sandflies that are infected. Leishmania's reservoirs can vary by region but include humans, sloths, marsupials, rats, hyraxes, and gerbils, as well as domestic dogs. Rarely, blood transfusions, contaminated needles, and pregnant women to babies transmit leishmaniasis (Capelli *et al*., 2004; Lourdes *et al*., 2009).

2.2 Symptoms

Following an infectious sandfly bite, symptoms can appear weeks or months later. After a sandfly bite, a papule that grows and eventually turns into an ulcer is the first sign of cutaneous leishmaniasis. It frequently gets a raised edge and a central crater, resembling a volcano. There could be one or more lesions, and there might be enlarged lymph nodes close by. On rare occasions, leishmaniasis species, which are mostly prevalent in Central and South America, might harm mucous membranes in the mouth and nose in addition to the initial cutaneous sore on the face. The symptoms of visceral leishmaniasis include weight loss, anemia, weakness, enlarged spleen and liver, and recurrent fever. If treatment is not received, this kind of leishmaniasis, which is the most severe, can be fatal (Scarpini *et al*., 2022; Karen *et al*., 2004).

2.3 Treatment

For half a century, pentavalent antimony (sodium stibogluconate or meglumine antimonate) has been the cornerstone of antileishmanial treatment. This was once used for all manifestations of the illness. The antimonial's mode of action starts from their disruption of the bioenergetic processes of amastigotes of Leishmania. These products attach to various parasite proteins and block their activity, especially those enzymes that are involved in fatty acid oxidation and glycolysis. The intracellular ATP levels necessary for Leishmania's survival are reduced because ADP phosphorylates to ATP using NADH produced by glycolysis and the citric acid cycle. However, there are adverse effects from the antimonials including stiff joints, pain at the injection site, gastrointestinal issues, cardiotoxicity, and in certain circumstances, insufficiency of the liver and kidneys. Recently, liposomal amphotericin B has been used as a preferred medication for visceral illness, replacing pentavalent antimony. Pentamidine stops oxidative phosphorylation and nucleic acid incorporation into RNA and DNA, which stops the creation of proteins and phospholipids and prevents protozoa from growing. However, in a sizable percentage of patients, it results in major adverse effects like shock, hypoglycemia, and death. There are reports of high recurrence rates and widespread resistance to it in India (Peter *et al*., 2009).

An alkyl phosphocholine analogue known as miltefosine (hexadecylphosphocholine) has demonstrated good activity against Leishmania both *in vitro* and when given orally to animals. Miltefosine has been demonstrated to change the composition of phospholipids and sterols and to inhibit Leishmania's growth. There have been reports of oral miltefosine's effectiveness and tolerance for treating Indian visceral leishmaniasis. In areas where parasites are resistant to present treatments, it might be useful. A T-helper subtype 1 cytokine called interferon-gamma is employed to enhance host defenses against Leishmania parasites. It has been reported that many alkaloids have good antileishmanial action (Thakur and Dedet, 2001).

The present treatment for leishmaniasis has numerous drawbacks, such as issues with low efficacy, extremely harmful side effects, and developing drug resistance. Antimonial and amphotericin B, the first-line treatments for leishmaniasis, must be administered intravenously over an extended period, which has a detrimental effect on patient compliance. A significant factor is the high cost of some of the more recent treatments, including the lipid formulations of amphotericin B, given that leishmaniasis primarily affects people in developing nations. Miltefosine is a novel medication that has a poor therapeutic index and is teratogenic. Therefore, there is a need for novel antileishmanial medications (Bhuwan *et al*., 2009).

3. Review of Ayurveda herbs that used in the management of leishmaniasis

Although the term "kala-azar" is not used in Ayurveda, it describes three diseases, visamajvara (a type of fever), plihodara/pliharoga (splenomegaly), and raktaja krimi (microorganism in blood), which are similar to Indian kala-azar and appear to be appropriately correlated based on their etiology, prognosis, symptomatology, and treatment. The symptoms of plihodara syndrome include an abnormally enlarged spleen (the organ that produces blood cells), anorexia, thirst, body aches, lethargy, cough mild fever, abdominal pain, reddish or abnormal tinge, appearance of green, blue, or yellow streaks on abdomen, and moderate to severe anemia. Kala-azar can be effectively treated with ayurvedic herbs like Guduci (*Tinospora cordifolia*), Katuki (*Picrorhiza kurroa*), Daruharidra (*Berberis aristata*), Kumari (*Aloe barbadensis*), and Earanda (*Ricinus communis*), *etc*. These herbs have no side effects and naturally treat the illness (Parameswarapa, 2019).

3.1 *Tinospora cordifolia*

T. cordifolia (Figure 1) commonly named "Guduchi" in Sanskrit belonging to the family Menispermaceae, is a significant medicinal plant that is acknowledged as being an essential part of most ayurvedic remedies. Numerous medicinal benefits of this plant's extracts have been demonstrated, including nephroprotective, antihepatotoxic, antipyretic, anti-inflammatory, antiarthritic, antimalarial, aphrodisiac, and antiallergic effects (Shastry, 2004a). When *T. cordifolia* and cisplatin were combined, the Th1 type of immune response was preferentially activated, as seen by increased levels of IFN-γ and IL-2, while Th2 specific cytokines, IL-4 and IL-10, showed a mild reduction. Additional evidence supporting Th1 polarisation came from higher IgG2a levels compared to IgG1 and a stronger DTH

(delayed type hypersensitivity) response. Various chemical compounds which belong to different classes such as alkaloids, diterpenoids, lactones, glycosides, steroids, sesquiterpenoids, phenolics, and aliphatic compounds having immunomodulatory activities have been isolated from this plant (Upadhyay *et al*., 2010). This implies that *T. cordifolia* therapy could be a vital countermeasure for the negative effects of cisplatin. Therefore, in the future, this could be a novel combination to combat visceral leishmaniasis (Sachdeva *et al*., 2014).

3.2 *Picrorhiza kurroa*

Traditionally, *Picrorhiza kurroa* (Figure 2) belongs to family, the Scrofulariaceae and has been considered one of the most useful medicinal herbs. *P. kurroa* is used in traditional and folklore medicine for a variety of conditions, such as laxative, cholagogue, liver stimulatory, breathing difficulties, digestion, allergy, tuberculosis, skin conditions, burning sensation, chronic recurrent fever, jaundice, heart problems, problems related to blood and digestion, prediabetes and obesity. Glycosides, alkaloids, cucurbitacins, iridoids, phenolics, and terpenes are the phytoconstituents in *P. kurroa* that have demonstrated encouraging pharmacological potential. *P. kurroa* screening is crucial to finding new chemicals that may treat chronic illnesses like cancer, diabetes, cardiovascular disease, respiratory conditions, and hepatoprotective diseases (Lucas, 2008a). Picroliv is a standardized combination of iridoid glycosides made from *P. kurroa* root and an alcoholic extract of root. The effects of sodium stibogluconate alone and in combination with picroliv (12.5 mg/kg x 7 days oral) on the hepatic marker enzymes, lipid peroxidation, and parasitemia of golden hamsters during *L. donovani* infection were investigated. The findings showed that picroliv had a notable hepatoprotective effect on biochemical markers as well as significant antileishmanial activity. These findings suggest that picroliv can be used as a supplement to chemotherapy or in combination therapy with sodium stibogluconate and kala-azar to increase the effectiveness of antileishmanial (Mittal *et al*., 1998).

3.3 *Nyctanthes arbortristis*

Nyctanthes arbortristis (Figure 3) belongs to the family Oleaceae, popularly known as "Parijata". *N. arbortristis,* is one of several plants that are frequently used in traditional Indian medicine to cure a wide range of human diseases, being used as a laxative, rheumatism, skin conditions, and sedative; it also has anthelminthic and antipyretic properties (Shastry, 2004b). Night jasmine leaf extracts showed notable efficacy against *L. donovani* (Ag83, axenic promastigotes). The golden hamster with *L. donovani* infection was also cured by the bioactive fraction of *N. arbortristis* (Sharmila, 2013). The plant's crude extracts and isolated components have demonstrated therapeutic activity against leishmaniasis, viral infections, inflammation, and inflammation as well as acting as an immunostimulant. The primary category of physiologically active substances consists of iridoid glucosides, such as arbortristosides A, B, and C found in seeds. These chemicals have antiviral, anticancer, anti-inflammatory, antileishmania, and immunomodulatory properties. There have been reports of the antileishmanial, anti-cancer, and anti-inflammatory properties of calceolarioside A, 4-hydroxyhexahydrobenzofuran-7-1, and β-sitosterol derived from leaves (Jyoti and Anirban, 2013).

3.4 *Desmodium gangeticum*

Desmodium gangeticum (Figure 4) belongs to the family Fabaceae, known as Shalaparni in Sanskrit. Many ailments, including typhoid fever, piles, inflammations, bronchitis, asthma, vomiting, dysentery, and hemicrania, have been treated with this plant in Ayurveda (Lucas, 2008b). It has been reported that a 50 µg/ml concentration of this plant's methanolic extract exhibited antileishmanial action *in vitro* against a visceral Leishmania strain. Chemoprophylactic and chemotherapeutic evaluations of the crude ethanolic extract of the Indian medicinal plant, *D. gangeticum* (A001) and its three fractions-hexane (F002), n-butanol (F003), and aqueous (F004) were analyzed in hamsters with visceral leishmaniasis. At a dosage of 250 mg/kgx2, ethanolic extract demonstrated 41.2+/-5.3% reduction of parasite proliferation on the 7th day and +7 of the *L. donovani* challenge. When given at the same dosing schedule, its n-butanol fraction had more efficacy than the ethanolic extract, measuring 66.7+/-6.1% inhibition. However, no prophylactic action was shown in the other two portions. F003 showed significant ($p<0.001$) non-specific resistance to peritoneal macrophages against Leishmania infection. When tested against hamsters that had an established *L. donovani* infection, F003 also showed some mild antileishmanial activity; however, the other three fractions were unable to significantly limit the growth of the parasite. According to these results, this plant may be useful both therapeutically and prophylactically against Leishmania infection (Singh *et al*., 2005). Two glycolipids with antileishmanial and immunomodulatory properties were found in *D. gangeticum*: glycosphingolipid (cerebroside) and aminoglucosyl-glycerolipid. It was discovered that aminoglucosyl-glycerolipid was distinct (Pushpesh *et al*., 2005).

3.5 *Berberis aristata*

B. aristata (Figure 5) often referred to as "Daruhaldhi" in Hindi belongs to the family Berberidaceae. It is reported to have characteristics similar to those of turmeric (Divya *et al*., 2023; Vidyavathi *et al*., 2023). It is reported to have characteristics similar to those of turmeric. Indian barberry and its extract "rasot" are said to be deobstruent and alterative; they are used to treat skin conditions, diarrhoea, menorrhagia, jaundice, and eye diseases (Praksh and Harini, 2021a). Alkaloids are the primary plant chemicals that exhibit the strongest antileishmanial effects. The primary isoquinoline alkaloid found in *Berberis* (*B. vulgaris* and *B. aristata*) is berberine, the primary analog of quinoline and isoquinoline. It has been reported to exhibit antileishmanial action in *L. donovani*, *L. amazonensis*, and *L. braziliensis* (Luis and Manuel, 2001). The anti-inflammatory quaternary isoquinoline alkaloid berberine chloride (BER, 1,8,13- á-tetra-hydro-9,10-demethoxy-2,3-(methyl-ene-dioxy)-berberium chloride) is found in medicinal plants (*Berberis vulgaris* and *Berberis aristata*). It has been shown several biological effects, including antileishmanial activity (Calvo *et al*., 2020).

3.6 *Aloe barbadensis*

Aloe vera (Figure 6) also known as Ghrita kumari in Sanskrit belongs to family the Liliaceae and is the most abundant source of health benefits for humans. It possesses a wide range of antimicrobial, anti-inflammatory, immunomodulatory, antiseptic, anthelminthic, and antioxidant qualities (Praksh and Harini, 2021b). Promastigotes from strains that cause cutaneous, mucocutaneous, and visceral leishmaniasis were responsive to *Aloe vera* leaf exudate (AVL), and their IC_{50} ranged from 100 to 180 microg/ml, regardless of the disease's manifestation. Host macrophage activation induced by AVL

was demonstrated by an increased release in reactive oxygen species, which was mitigated by preincubation with free radical scavengers. Altogether, our observations suggest that AVL is a potent antileishmanial drug that deserves more pharmacological research due to its direct leishmanicidal activity, which can be further boosted by activating host macrophages (Dutta *et al*., 2007). The presence of phenol, alkaloid, and saponin in the plant may be the reason for the good antileishmaniasis activity of the methanol extract of *Aloe vera* (Tesfaye *et al*., 2016).

3.7 *Ricinus communis*

The roots of Earanda (*R. communis.)* belong to the family, Euphorbiaceous (Figure 7) and are used in Ayurveda medicine to cure a variety of conditions, including rheumatism, inflammation, back pain, abdominal diseases, fever, *etc*. (Shastry, 2004c; Pradeep *et al*., 2022). There have been reports of *R. communis* as a potential replacement for sandfly management. Sandfly mortality is increased and parasite stomach abnormalities are caused when sandflies feed on *R. communis*. The excellent efficacy of *R. communis* ethyl acetate extract against *L. infantum* (amastigotes and promastigotes), as well as its minimal cytotoxicity towards murine monocytic cells, were discovered through an *in vivo* investigation. Furthermore, the antagonistic action of *R. communis* on cutaneous leishmaniasis was elucidated by Bahmani *et al*. (2017). The antileishmanial activity of *A. indica* and *R. communis* combination therapy was superior to that of monotherapies (Wafaa *et al*., 2022). Rana *et al*. (2012) found that the presence of gallic acid, quercetin, gentistic acid, tannins, and alkaloids in castor contributes to its antioxidant, anti-inflammatory, antidiabetic, antitumor, larvicidal, antinociceptive, and antiasthmatic activities.

3.8 *Ferula asafetida*

Asafetida (Figure 8) belongs to family, the Apiaceae and is described in Ayurveda as a useful treatment for a variety of conditions, including hysteria, neurological disorders, whooping cough, pneumonia, and bronchitis in children. It is also thought to have aphrodisiac properties (Praksh and Harini, 2021c). After being separated from the spleens of mice, amastigotes were converted into promastigotes in Novy-Nicolle-Mac Neal (NNN) medium, which was enhanced with 20% heat-inactivated fetal calf serum (FCS), penicillin (100 U/ml), and streptomycin (100 µg/ml) at 25°C. The parasites were initially concentrated at a constant density and then placed into screw-capped vials with 5 ml of RPMI1640 medium. It was mixed with various doses of 2.5, 5, 10, and 20 µg asafetida, each of which was added three times. Control was also included in every run. Using the slide and the enzyme-linked immunosorbent assay (ELISA) techniques, the mortality of parasitoids was determined. Asafetida stopped parasite growth in both stationary and logarithmic phases after 72 h. According to the ELISA assessment, there was a significant decrease in parasite vitality after 48 hours ($p<0.05$). The findings indicate that asafetida may inhibit the growth and vitality of parasites, and that leishmaniasis may benefit from the usage of asafetida (Bafghi *et al*., 2014). The asafoetida plant has the potential to produce effective medications against leishmaniasis due to its composition, which includes di-,tri-,tetra-sulfide, coumarin derivatives, camuonephrole, episamarcandine, amblipernine, carnephrole, azafoetidine, froxolicin, azafoetidinole, saradaferine, 1, 8 cineole, scopodreniole, semen, sabinine, cineole, inaleole, eojenole, farenzole, borneol, allicin, acid glycerisic, emetine, and cephalin (Bahmani *et al*., 2017).

3.9 *Allium sativum*

Garlic (Figure 9) is known as Lasuna and belongs to the family Amaryllidaceae, which signifies, the destroyer of diseases. Worldwide, people use garlic as a food and condiment. It has also been used as a preventative and therapeutic measure for tuberculosis, cholera, typhoid fever, and gastrointestinal tract disorders. Garlic's antiparasitic activity is mostly attributed to allicin (diallyl thiosulfinate), diallyl disulfide, and ajoene [(E, Z) 4, 5, 9-trithiadodeca-1, 6, 11-triene-9-oxide], according to a literature review on phytochemical analysis (Lucas, 2008c). The physiological alterations impact thiol homeostasis and cause disruption of the plasma membrane, ultimately leading to the parasite's death, which may be the cause for the antiparasitic (antileishmanial) action. It is interesting to note that in addition to their *in vitro* antileishmanial activity, garlic constituents have also been shown to have immunomodulatory effects, which can be attributed to their ability to change the cytokine response to a Th-1-type pattern and thereby strengthen the host's immunity against leishmaniasis (Foroutan *et al*., 2017). The potent antimicrobial component of *A. sativum*, allicin (diallyl thiosulfinate), significantly inhibits the growth of leishmanial cells. The injection of pure allicin into the culture wells hindered the growth of *L. mexican* and *L. chagasi*. Ajoene, fresh and boiling extracts of *A. sativum*, diallyl disulfide, diallyl trisulfide, and allyl sulfide were also investigated as possible antileishmanial chemotherapeutic drugs (McClure *et al*., 1996).

3.10 *Azadirachta indica*

Azadirachta indica (Figure 10), also known as Neem, belongs to the family Meliaceae and is one such plant with several therapeutic uses. All the neem plant parts are used to make various medicinal compounds (Shastry, 2004d; Antony *et al*., 2023). Its qualities include immunological modulation, anti-inflammatory, and anticarcinogenic. A promising function in disease control was addressed by testing neem leaf crude fractions for antileishmanial activity on *L. amazonensis*. Given its effectiveness against bacteria resistant to many drugs, Neem may also be able to combat drug-resistant forms of *L. donovani* (Alti *et al*., 2015). It has a significant concentration of the following active ingredients: quercetin, sodium nimbinate, azadirachtin, nimbin, and nimbidin. Numerous fatty acids are also included in it, including linoleic acid, palmitic acid, stearic acid, and oleic acid. Which are responsible for hepatoprotective, antioxidant, immunostimulant, antileishmanial, and antimalarial activity (Veitch *et al*., 2007).

Figure 1: ***T. Cordifolia***

Figure 2: *P. kurroa*

Figure 3: *N. arbartristis*

Figure4: *D. gangeticum*

Figure 5: *B. aristata*

Figure 6: *A. barbadensis*

Figure 7: *R. cummunis*

Figure 8: *A. sativum*

Figure 9: *F. asafetida*

Figure 10: *A. indica*

4. Conclusion

Leishmaniasis is still unmanageable even with an extensive knowledge of its epidemiology. Leishmaniasis is one neglected protozoan disease of public health concern that deserves more attention and time from researchers worldwide. Finding the most effective surveillance system and control strategies to lower the death and morbidity rate, appropriately controlling vectors, identifying and combating risk factors, and developing a safe, non-invasive, quick, and affordable treatment should all be considered the most important steps toward achieving satisfactory control and eventual complete eradication of leishmaniasis from specific developing countries. According to *in vitro* and *in vivo* animal experimental research, a variety of plant extracts have intriguing antileishmanial capabilities, as demonstrated in the current review. To validate their actions, it is imperative to emphasize the need to translate the findings from both *in vitro* and *in vivo* research on the efficacy of plant extracts, metabolites, or formulations against various Leishmania species to clinical settings.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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