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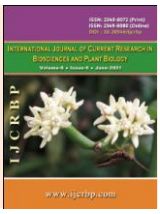

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Recent updates on leishmaniasis: Kala-azar outbreak, risk factors and herbal treatment

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Abstract

Leishmaniasis is one of the infectious neglected tropical diseases caused by a protozoan parasite vector of genus *Leishmania* which is transmitted to humans through an infected blood-sucking sandfly. Leishmaniasis is prevalent in tropical and temperate regions of world which is fatal and life threatening if ignored and untreated. The current outbreak of coronavirus (SARS-CoV-2) disease (Covid-19) with Kala Azar fever followed by mucormycosis is major health issue killing many people in India. Leishmaniasis is transmitted through the bite of female sand flies infected with the protozoan. Kala Azar is a hyper endemic tropical disease for which no vaccine has been approved yet. However, many drugs that are available for the treatment of Leishmaniasis diseases possess serious side effects and drugs are active only in the acute phase of the disease Kala Azar. Another major limitation of existing drugs are severe toxicity with side effects and drug resistance. The emergence of drug resistance has created the main hindrance for Kala Azar control with one critical target in the state of Bihar in India. Therefore, there is an urgent need to search for cheaper, more effective, easily available and less toxic chemotherapeutic agents for combating Leishmaniasis. Therefore, herbal medicines without any side effects play an important role in controlling human health disorders and infectious diseases, Leishmaniasis (Kala Azar). This review paper presents current updates of three different clinical syndromes of leishmaniases disease, control measures, risks and herbal medicine treatment strategies.

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Introduction

Leishmaniasis is known as the disease of the poverty and poor people with limited health facilities (Brindha et al., 2021; Mann et al., 2021; Karimi et al., 2021; Boelaert et al., 2009; Alvar et al., 2006, 2012; Rijal et al., 2019; Singh et al., 2006, 2010a, 2010b, 2016a, 2016b; Sridhar, 2017; Moulik et al., 2021). The term leishmaniasis refers to a diverse group of syndromes caused by protozoa of the genus *Leishmania*, in the

Leishmania and *Viannia* subgenera (Mann et al., 2021; Herwaldt, 1999; Murray et al., 2005; Singh et al., 2016; Aronson et al., 2016; Croft and Olliaro, 2011; Karimi et al., 2021; Burza et al., 2018). One billion people are at risk of infection across 98 countries worldwide, with over 1.5 million new cases and 20,000–40,000 deaths reported each year (Alvar et al., 2012; Hotez, 2018; Brindha et al., 2021; Mann et al., 2021; Ashwin et al., 2021). Acccording to WHO, leishmaniasis is one of the neglected tropical disease caused by the different species of leishmania, an obligate intracellular protozoan parasite (Ashwin et al., 2021; Brindha et al., 2021; Mann et al., 2021; Rijal et al., 2019; Murray et al., 2005; Rahimi et al., 2020; Cartuche et al., 2020; Herwaldt, 1999; Singh et al., 2016a, 2016b; Zeleke et al., 2021; Croft et al., 2006; Tejaswi and Rajan, 2020; Dye and Wolpert, 1988). Leishmania are the obligate intracellular parasites existing in two morphologic forms: Promastigote and Amastigote (Ashwin et al., 2021; Mann et al., 2021; Tejaswi and Rajan, 2020; Herwaldt, 1999; Murray et al., 2005; Tiuman et al., 2011). The transmission of *Leishmania* parasites is largely influenced by the characteristics of the vector involved in the transmission (Mann et al., 2021; Brindha et al., 2021; Rijal et al., 2019; Murray et al., 2005; Aronson et al., 2016; Dye and Wolpert, 1988; Hirve et al., 2016, 2017; Ahmed et al., 2018; Tejaswi and Rajan, 2020; Zeleke et al., 2021). The Leishmania promastigote are transmitted by sand fly to vertebrate hosts e.g. Canines, marsupials, edentates and rodents (Mann et al., 2021; Tejaswi and Rajan, 2020; Rijal et al., 2019; Aronson et al., 2016). Leishmaniasis is a vector-borne protozoan disease caused by an intracellular parasite which globally affected 350 million people and found endemic in 98 countries, India, Bhutan, Sri Lanka, Nepal, Bangladesh, Indonesia, Pakistan, East African countries including Sub-Saharan Africa, Ethiopia, Eritrea, Somalia, South Sudan and North Sudan, Nigeria, Egypt, South America, Peru, Syria, Brazil, Iraq, Kenya Iran, Saudi Arabia, Middle East, and South East Asia (Karimi et al., 2021;Mann et al., 2021; Priyamvada et al., 2021; Rijal et al., 2019; ; Brindha et al., 2021; Murray et al., 2005; Alvar et al., 2012; Zeleke et al., 2021; Tejaswi and Rajan, 2020).

Leishmaniasis is caused by the protozoan parasites which are transmitted by the bite of infected female Phlebotomine sandflies (Mann et al., 2021; Mondal et al., 2018; Rijal et al., 2019; Sridhar, 2017; Murray et al., 2005; Kamhawi, 2006). The parasite is then internalized via macrophages in the liver, spleen, and bone marrow (Rijal et al., 2019; Tejaswi and Rajan, 2020; Karimi et al., 2021). Over 90 sandfly species are known to transmit leishmania parasites (Priyamvada et al., 2021; Rijal et al., 2019; Karimi et al., 2021; Brindha et al., 2021;Mann et al., 2021;Murray et al., 2005; Kamhawi, 2006; Croft et al., 2006; Croft and Olliaro, 2011).

The outbreak of leishmaniasis disease is mainly due to poor hygienic conditions, malnutrition, population displacement, poor housing, a weak immune system and lack of financial resources in rural areas where people live below the poverty line (Karimi et al., 2021; Mann et al., 2021; Rijal et al., 2019; Murray et al., 2005; Boelaert et al., 2009;Alvar et al., 2006; Zeleke et al., 2021; Tejaswi and Rajan, 2020). Leishmaniasis disease is also linked to rural-urban migration, agro industrial environmental changes such as deforestation, building of dams, irrigation schemes and urbanization, agricultural occupations, cattle grazing and seasonal migration of farmers and daily labourers (Karimi et al., 2021; Rijal et al., 2019; Murray et al., 2005; Zeleke et al., 2021; Mann et al., 2021; Tejaswi and Rajan, 2020). The hosts can be humans but also rodents, dogs, and other mammals, and great diversity of immune response exists depending on the host considered (Karimi et al., 2021; Murray et al., 2005; Zeleke et al., 2021; Tejaswi and Rajan, 2020; Mann et al., 2021; Cameron et al., 2016). The number of leishmaniasis disease cases is increasing globally at an alarming rate. Another major concern is the current outbreak of coronavirus (SARS-CoV-2) disease (Covid-19) pandemic will also hinder the progress of drug development and delivery therapeutic approach to leishmaniasis disease. Therefore, people suffering from leishmaniasis with Covid-19 pandemic is a very serious life threatening issue and challenging too. Therefore, combination of existing or repurposed drugs is a new approach to combat the deadly leishmaniasis. This approach is also not successful due toxicity and drug resistance issue.

There are three different clinical syndromes of leishmaniases, 1) Visceral leishmaniasis (VL) (also known as Kala-Azar), 2) Cutaneous leishmaniasis (CL), 3) Mucocutaneous leishmaniasis (ML) (Brindha et al., 2021; Karimi et al., 2021; Mann et al., 2021; Moulik et al., 2021; Rijal et al., 2019; Murray et al., 2005; Singh et al., 2006, 2010a, 2010b, 2016; Zeleke et al., 2021; Tejaswi and Rajan, 2020; Aronson et al., 2016; Tiuman et al., 2011). For all the three forms of leishmaniasis, the infection can range from asymptomatic to severe (Mann et al., 2021; Murray et al., 2005; Herwaldt, 1999;

Karimi et al., 2021). Cutaneous and mucosal leishmaniasis can cause substantial morbidity, whereas visceral leishmaniasis (VL) (Kala Azar) can be life threatening and killed many people if it is not detected and treated at the early stage (Priyamvada et al., 2021;Mann et al., 2021; Kumar et al., 2020a, 2020b; Chappuis et al., 2007; Medley et al., 2015; Rijal et al., 2019; Murray et al., 2005; Karimi et al., 2021; Sundar et al., 2018; Tejaswi and Rajan, 2020; Sundar and Murray, 2005; Sundar et al., 2002, 2007; Zeleke et al., 2021). Therefore, treatment of leishmaniasis can be challenging (Rijal et al., 2019). Visceral leishmaniasis (VL) is endemic and common public health problem in the Bihar, West Bengal, Uttar Pradesh state, India (Priyamvada et al., 2021; Mann et al., 2021; Hasker et al., 2010; Kumar et al., 2020; Sundar et al., 2018; Rijal et al., 2019; Singh et al., 2006, 2010a, 2010b, 2016a, 2016b; Bora, 1999; Peters and Prasad, 1983). Several pharmaceutical research groups have invested heavily in discovering a drug targeting *Leishmania* parasites.

This review paper updated the recent developments in controlling the outbreak of different clinical forms of leishmaniasis. There are many medicinal plants with anti-protozoan activity could be used as an age old weapon for controlling leishmaniasis. Therefore, in near future there is a ray of hope for the eradication of this deadly disease leishmaniasis by using herbal therapy. This review paper also summarized the various therapeutic strategies that have been adopted in the past and present for the treatment of various clinical forms of leishmaniasis.

Visceral leishmaniasis (VL) or Kala-azar

Visceral Leishmaniasis (VL) or Kala Azar is a vector-borne disease caused by the protozoan parasite *Leishmania donovani*, *Leishmani infantum*, or *Leishmania arachibaldi*, and transmitted by the female sand fly *Phlebotomus argentipes* bite (Brindha et al., 2021; Mann et al., 2021; Priyamvada et al., 2021; Rijal et al., 2019; Medley et al., 2015; Chappuis et al., 2007; Boelaert et al., 2009; Hirve et al., 2016, 2017; Alvar et al., 2006; Sundar et al., 2018; Cameron et al., 2016). Visceral leishmaniasis is a chronic infection, associated with the high mortality and morbidity (Brindha et al., 2021; Priyamvada et al., 2021; Mann et al., 2021; Sundar et al., 2018; Kumar et al., 2020a, 2020b). A potential concern is the recent identification that 19.5% of Iraq-deployed American soldiers have blood testing which suggests that they have asymptomatic visceral leishmaniasis, including 1% with parasitemia as measured by polymerase chain reaction, persisting up to a decade after return to the U.S (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). It is a life-threatening infectious disease affecting many people around the globe and killing 50,000 individuals a year (Rijal et al., 2019; Mann et al., 2021; Singh et al., 2016a, 2016b; Peters and Prasad, 1983; Boelaert et al., 2009; Bora, 1999; Tejaswi and Rajan, 2020; WHO, 2005). Another major issue is visceral leishmaniasis (VL) (Kala Azar) is a very common and opportunistic infection in HIV patients due to the poor immunity or other causes of cell-mediated immunosuppression (Cota et al., 2013; Albuquerque et al., 2014; Jarvis and Lockwood, 2013; Rijal et al., 2019). Therefore, WHO declared that Kala Azar (Visceral leishmaniasis) (VL) remained one of the top parasitic disease with the outbreak and mortality potential (Mann et al., 2021; Rijal et al., 2019;Alvar et al., 2006, 2012; Zeleke et al., 2021; Chappuis et al., 2007; Hirve et al., 2016, 2017; Kumar et al., 2020a, 2020b). Visceral leishmaniasis (VL) is a common public health problem and 95% of the cases have been reported in Bihar state, India (Brindha et al., 2021; Cameron et al., 2016; Medley et al., 2015; Kumar et al., 2020a, 2020b; Singh et al., 2006, 2010a, 2010b; Rijal et al., 2019; Hirve et al., 2016, 2017; Sundar et al., 2002, 2007; Mubayi et al., 2010; Chappuis et al., 2007). In addition, visceral leishmaniasis (VL) disease was also detected in West Bengal and Eastern UP states of India (Priyamvada et al., 2021; Rijal et al., 2019; Ganguly et al., 2006; Sundar and Murray, 2005; Sundar et al., 2007; Mubayi et al., 2010; Tejaswi and Rajan, 2020; Kumar et al., 2020a, 2020b; Dye and Wolpert, 1988). The current spatial distribution of Visceral Leishmaniasis (VL) or Kala azar is mostly confined to a limited area in four middle eastern Indian states (Bihar, Jharkhand, Uttar Pradesh, and West Bengal) (Kumar et al., 2020a, 2020b). Hence, in 2015, the Director General of Health Services (DGHS, New Delhi) and the National Vector Borne Disease Control Program (NVBDCP, New Delhi) assigned the Vaishali District (the second most Visceral Leishmaniasis (VL) or Kala Azar endemic district in Bihar) to ICMR-Rajendra Memorial Research Institute of Medical Sciences (ICMR-RMRIMS; Patna) to reduce the Visceral Leishmaniasis (VL) or Kala Azar incidence to below 1 case per 10,000 people in all infected blocks (Kumar et al., 2020a, 2020b; Rijal et al., 2019).

Visceral leishmaniasis (VL), which reflects dissemination of leishmania parasites throughout the

reticuloendothelial system, is potentially life threatening without treatment (Mann et al., 2021; Priyamvada et al., 2021; Rijal et al., 2019; Aronson et al., 2016; Zeleke et al., 2021; Dye and Wolpert, 1988; Singh et al., 2016a, 2016b). Visceral leishmaniasis (VL) is potentially life threatening and requires prompt evaluation and treatment (Kumar et al., 2020a, 2020b ; Rijal et al., 2019; Aronson et al., 2016; Singh et al., 2006, 2010a, 2010b; Hirve et al., 2016, 2017). Further research and development of antifungal drugs related work has been done at 1) London School of Hygiene and Tropical Medicine, London, UK, 2) Department of Parasitology, Hadassah Medical School, Jerusalem, Israel, 3) Central Drug Research Institute, Lucknow, India. In India, the sample collection from the infected patients, treatment care and hopitalization has been taken care by in joint collaboration with Medicines-SANS-Frontiers (MSF), WHO, and Rajendra Memorial Research Institute of Medical Sciences (ICMR), Patna, Bihar state, India and Sadar Hospital (MSF), Hajipur, Vaishali district, Bihar state, India (Priyamvada et al., 2021; Kumar et al., 2020a, 2020b; Rijal et al., 2019; Sundar et al., 2002, 2007; Mubayi et al., 2010; Hasker et al., 2010; Singh et al., 2006, 2010a, 2010b).

The leading most productive Indian organizations contributing to Leishmaniasis research (Ahmed et al., 2018) were 1) Banaras Hindu University, Varanasi (S. Sundar, & J. Chakravarty), 2) Indian Institute of Chemical Biology, Kolkata (S. Roy, and N Ali), 3) Central Drug Research Institute, Lucknow (A. Dubey), 4) Rajendra Memorial Institute of Medical Sciences, Patna (P. Das, K. Pandey, S. Das, VNR Das, V Kumar, and S. Bimal), 5) All India Institute of Medical Sciences, New Delhi, 6) Postgraduate Institute of Medical Education and Research, Chandigarh, 7) National Center for Cell Science, Pune, 8) Institute of Pathology, New Delhi (P. Salotra), 9) Jadavpur University, Kolkata, 10) Jawaharlal Nehru University, New Delhi (R. Madhubala), 11) Indian Institute of Technology, Guwahati (VK Dubey), 12) National Institute of Pharmaceutical Education and Research, Mohali, 13) Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, 14) Bose Institute, Kolkata, and 15) Institute of Postgraduate Medical Education and Research, Kolkata during 2008-17 (Ahmed et al., 2018; Kumar et al., 2020a, 2020b).

Laboratory diagnosis of Leishmaniasis can be made by 1) Demonstration of parasite, 2) Serological tests e.g., rK39 strip test and direct agglutination test, 3) Antigen detection, 4) Molecular diagnosis, 5) Leishmania skin test (LST) or Montenegro skin test, 6) Lymphocyte proliferation assay (LPA), 7) Western blot, 8) Isoenzyme analysis, 9) Excreted factor, 10) DNA based methods, 11) Polymerase Chain Reaction (PCR), 12) Single Nucletide polymorphism (SNP), 13) IgG1-potential biomarker of post chemotherapeutic relapse diagnostic test, 14) Immunochromatographic rapid diagnostic tests for visceral leishmaniasis (Mann et al., 2021; Priyamvada et al., 2021; Mondal et al., 2016; Adams et al., 2018; Vallur et al., 2015; Bhattacharyya et al., 2014; Kumar et al., 2020a, 2020b; Chappuis et al., 2007; Cunningham et al., 2012; Boelaert et al., 2008; 2014; Rijal et al., 2019). In another major development, *Leishmania* antigen ELISA on urine detects active asymptomatic infection, requires a non-invasive sample (Owen et al., 2021). Therefore, this test may be of benefit for monitoring transmission and surveillance in an elimination setting in combination with serology (Owen et al., 2021). Development of an antigen detection test in a rapid diagnostic test (RDT) format would be of benefit to the elimination campaign (Owen et al., 2021).

Humans are considered as the only reservoirs of infection. It is fatal if left untreated. The incubation period is usually 2-4 months. After an incubation period of 2-4 months, patients develop a syndrome characterised by fever, splenomegaly, wasting, and anaemia (Rijal et al., 2019; Mann et al., 2021; Boelaert et al., 2009;Alvar et al., 2006; Singh et al., 2016a, 2016b; Mondal, 2016). Demonstration of parasites in a smear or culture of aspirate from spleen, bone marrow, or lymph node is required to confirm the diagnosis. Alternatively, serological evidence in a patient with recent onset of febrile splenomegaly in endemic areas will suffice (Rijal et al., 2019; Mann et al., 2021; Singh et al., 2016a, 2016b; Mondal, 2016).

Visceral leishmaniasis is characterized by pallor, hepato splenomegaly, lymphadenopathy, immunosuppressant and progressive weakness in the patient (Rijal et al., 2019; Boelaert et al., 2008; Tejaswi and Rajan, 2020; Adams et al., 2018; Vallur et al., 2015; Chappuis et al., 2007; Singh et al., 2006, 2010a, 2010b, 2016a, 2016b). Visceral Leishmaniasis (Kala-azar) is a disseminated protozoan infection which is characterized by irregular fever for long duration, large spleen and liver, anaemia, leucopoenia and progressive emaciation (Rijal et al., 2019; Chappuis et al., 2007; Boelaert et al., 2009;Alvar et al., 2006; Tejaswi and Rajan, 2020; Adams et al.,

2018; Mann et al., 2021; Kumar et al., 2020a, 2020b). It may lead to death if untreated. Failure to treat Visceral leishmaniasis (VL) successfully is often due to increased chemo resistance of the parasite (Rijal et al., 2019; Adams et al., 2018; Chappuis et al., 2007; Singh et al., 2016a, 2016b; Mondal, 2016; Tejaswi and Rajan, 2020). The clinical features on presentation reflect the chronicity and severity of the infection. The cardinal features are fever, hepatosplenomegaly and pallor which are present in about 95% cases. Double peak of temperature in 24 hrs is considered highly suggestive of Kala-azar (Rijal et al., 2019; Boelaert et al., 2009; Alvar et al., 2006; Tejaswi and Rajan, 2020). The patient is not toxic and appetite is good. Sometimes there is epitasis and bleeding from gums (Rijal et al., 2019; Tejaswi and Rajan, 2020; Singh et al., 2016a, 2016b; Boelaert et al., 2009;Alvar et al., 2006; Mondal, 2016). Spleen enlarges progressively. Liver is also enlarged in 4/5th of cases. In chronic cases, there is anaemia, weight loss and emaciation (Rijal et al., 2019; Bhattacharyya et al., 2014; Chappuis et al., 2007; Sridhar, 2017; Olliaro et al., 2017; Boelaert et al., 2008) Patient may develop intercurrent infections of respiratory and gastrointestinal systems. A large number of patients developed darkening of the skin, especially on the face, hands and upper torso (Rijal et al., 2019; Bhattacharyya et al., 2014; Singh et al., 2016a, 2016b; Mondal, 2016; Chappuis et al., 2007; Boelaert et al., 2008; Gedda et al., 2020; Tejaswi and Rajan, 2020). In Asia, a single dose infusion of liposomal amphotericin B is the first treatment, with several combination regimens as alternatives. Around 5-10% of patients develop post-kala-azar dermal leishmaniasis (PKDL) within 6 months or more after the disease has apparently been cured (Moulik et al., 2021; Gedda et al., 2020; Kumar et al., 2020a, 2020b; Rijal et al., 2019; Boelaert et al., 2009; Alvar et al., 2006; Sridhar, 2017; Olliaro et al., 2017; Singh et al., 2016a, 2016b; Mondal, 2016; Bhattacharyya et al., 2014; Chappuis et al., 2007; Boelaert et al., 2008; Tiuman et al., 2011; Tejaswi and Rajan, 2020).

Pentavalent antimonials are presently first-line available treatment administered for both Visceral and Cutaneous leishmaniasis since 1945 (Tiuman et al., 2011; Tejaswi and Rajan, 2020). However, these drugs are becoming increasingly ineffective due to resistance (Gervazoni et al., 2020). The second choice agents are Amphotericin B and Pentamidine, solely apply for Visceral leishmaniasis (VL). The available and effective drugs against Visceral leishmaniasis (VL) include Sodium Stibogluconate (Pentostam®) and Meglumine Antimoniate, Amphotericin B Deoxycholate, Fungizone® and AmBisome® (Prajapati et al., 2011a, 2011b;Tejaswi and Rajan, 2020; Tiuman et al., 2011; Singh et al., 2010). Miltefosine (Impavido®) has been approved as the first oral drug (Tiuman et al., 2011; Mann et al., 2021; Sundar et al., 2002, 2007; Tejaswi and Rajan, 2020). Miltefosine is effective but expensive and teratogenic (DNDi, 2016; Gervazoni et al., 2020).

Paromomycin is the latest drug to be registered for use in India against Visceral leishmaniasis (VL) (Tiuman et al., 2011; Tejaswi and Rajan, 2020). The side effects associated with these drugs include significant toxicity, high cost and long treatment courses (Tiuman et al., 2011; Tejaswi and Rajan, 2020). Most of the commonly used drugs are toxic and do not cure, i.e., eliminate the parasite, from infected individuals (Tiuman et al., 2011; Tejaswi and Rajan, 2020). Failure to treat Leishmaniasis successfully is often due to increased chemo resistance of the parasite (Moulik et al., 2021; Tiuman et al., 2011; Tejaswi and Rajan, 2020). A major problem is that many of these drugs were developed many years ago and some parasitic strains have become resistant to them (Moulik et al., 2021; Tiuman et al., 2011; Tejaswi and Rajan, 2020). Failure to treat leishmaniasis successfully is often due to increased chemoresistance of the parasite (Tiuman et al., 2011). However, spontaneous cure is the rule, the rate of recovery varies depending on the species of Leishmania, and may require months or years to complete healing (Tiuman et al., 2011).

In another major development in 2005, World Health Organization (WHO) supported and established a joint regional alliance to eliminate kala-azar in three endemic countries in South Asia, India, Bangladesh, and Nepal (Moulik et al., 2021; Rijal et al., 2019; Kumar et al., 2020a, 2020b; Singh et al., 2016a, 2016b; Mondal, 2016; Zijlstra et al., 2017). This WHO joint collaborated-kala-azar elimination programme has shown good progress in terms of controlling the disease, research and developmental activities. Therefore, this unique kala-azar elimination programme has been extended up to 2025 based on the local performance and outcome results (Kumar et al., 2020a, 2020b; Moulik et al., 2021; Rijal et al., 2019; Zijlstra et al., 2017). Furthermore, the kala azar elimination programme confirmed that the oral drug miltefosine and a rapid diagnostic test based on the rK39 antigen had a impact on early diagnosis and provided the best effective

treatment to reduce the disease burden (Moulik et al., 2021; Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014). The current rapid diagnostic test detects antibodies against rK39 antigen (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014; Kumar et al., 2020a, 2020b). Decreasing the time between onset of symptoms and diagnosis might helped to reduce the transmission (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014). The kala-azar elimination programme has been benefited greatly from this diagnostic test for the detection of cases (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014). The kala-azar elimination programme has also focused on vector control and improved the surveillance to reduce the transmission and improved case detection (Rijal et al., 2019; Kumar et al., 2020a, 2020b). Caution is needed as a resurgence of kalaazar is possible. However, kala-azar elimination programme did not target "elimination of the pathogen" and thus some transmission continued (Kumar et al., 2020a, 2020b ;Rijal et al., 2019; Zijlstra et al., 2017; Chappuis et al., 2007). According to Rijal and coworkers (2019), the number of kala azar disease cases in India seems to follow roughly 15 year cycles (Rijal et al., 2019). Therefore, "natural" fluctuation of the kala azar disease has made the disease is out of control in the endemic region (Dye et al., 1988; Rijal et al., 2019; Kumar et al., 2020a, 2020b). Local communities that had some herd immunity in the past may gradually be becoming fully susceptible (Le Rutte et al., 2018; Rijal et al., 2019). The concerning fact is that HIV patients are more vulnerable to the post-kalaazar dermal leishmaniasis (Zijlstra et al., 2017; Akuffo et al., 2018; Rijal et al., 2019). Patients suffering from HIV coinfected with kala azar might served as the reservoirs of infection, perpetuating transmission even when the elimination targets are reached. Treatments for both conditions are far from ideal (Akuffo et al., 2018; Mondal et al., 2018; Rijal et al., 2019; Bhattacharya et al., 2007, 2014).

The joint WHO- kala-azar elimination programme confirmed a single dose infusion of liposomal amphotericin B (AmBisome) as first line treatment in 2013 instead of miltefosine (Akuffo et al., 2018; Mondal et al., 2018; Bhattacharya et al., 2007; Rijal et al., 2019). AmBisome has shown greater efficacy and improved compliance, but it requires a strict cold chain (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014; Kumar et al., 2020a, 2020b). AmBisome has been used successfully in the attack phase of the programme in India. However, the entire programme (ie, primary kala-azar, relapses, post-kala-azar dermal leishmaniasis, and HIV-kala-azar cases) is now reliant on a single medicine AmBisome (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014). Paromomycin-miltefosine combination therapy is recommended as an alternative where a cold chain cannot be ensured (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014; Akuffo et al., 2018; Mondal et al., 2018). This regimen includes 10 days of injections with paromomycin. Miltefosine is potentially teratogenic, which limits its use in women (Rijal et al., 2019; Sundar et al., 2002; Boelaert et al., 2014; Akuffo et al., 2018; Mondal et al., 2018). AmBisome-miltefosine combination also reduced the treatment duration, relapses, and toxicity in patients with post-kala-azar dermal leishmaniasis and HIV coinfection (Rijal et al., 2019; Mann et al., 2021; Sundar et al., 2002; Boelaert et al., 2014; Akuffo et al., 2018; Mondal et al., 2018).

Artemisinin and its derivatives are another group of molecules that are reported to be effective for visceral leishmaniasis treatment (Brindha et al., 2021; Mann et al., 2021). Nanotechnology-based drug delivery or drug formulations were attempted to improve the efficacy and also to assure safety of drugs and found successful (Brindha et al., 2021; Gedda et al., 2020; Rahimi et al., 2020; Ray et al., 2021; Monteiro et al., 2019). These drug-loaded PLGA nanoparticles have shown a new perspective to drug administration with good pharmacological activity. Also, high efficacy has been reported with nanoformulations of amphotericin B (Brindha et al., 2021; Gedda et al., 2020; Rahimi et al., 2020; Ray et al., 2021; Monteiro et al., 2019). A recent in vitro study involved the use of an FDA-approved drug for malaria treatment halofantrine, for leishmaniasis treatment (Brindha et al., 2021; Mann et al., 2021). However, there are no molecular markers of drug resistance for Leishmania and testing for drug resistance is limited (Mann et al., 2021).

Measures to control vectors approach were also applied particularly in indoor residual spraying of insecticides in endemic villages reporting kala-azar cases (Mondal et al., 2013; Rijal et al., 2019; Sridhar, 2017; Le Rutte et al., 2018). The expensive durable wall lining has also shown promise in controlling sand fly density (Huda et al., 2016; Rijal et al., 2019). In addition to this, wall paint containing three insecticides, including a larvicide, and an insecticide repellent combination for canine leishmaniasis were also applied (Dumont et al., 2015;

Rijal et al., 2019). A toolkit for monitoring and evaluation of entomological interventions was also developed within the kala azar elimination programme (Rijal et al., 2019; WHO/TDR, 2010; Coleman et al., 2015). DDT spraying was also applied for the control of kala azar (Rijal et al., 2019; Coleman et al., 2015). Pyrethroid spraying has been shown to be effective in reducing sand flies in carefully controlled experiments (Rijal et al., 2019; Coleman et al., 2015; Poché et al., 2018 Chowdhury et al., 2017). However, field studies suggested that the level of vectors has not declined significantly in villages treated by indoor residual spraying (Poché et al., 2018; Rijal et al., 2019; Mondal et al., 2013). Spraying also requires a lot of equipment, is expensive, and is often not easily acceptable to communities, making it unsustainable in the long term (Rijal et al., 2019; Huda et al., 2016).

In view of these drawbacks, researchers looked for alternatives that were cost effective, had a longer period of efficacy, and were easy to use and sustain (Rijal et al., 2019). Trials in Bangladesh, India, and Nepal have shown reduction of sand fly density using re-impregnated commercial bed nets and long lasting insecticide treated bed nets (Rijal et al., 2019;Picado et al., 2010a, 2010b; Sridhar, 2017; Le Rutte et al., 2018; Huda et al., 2016). Two factors such as integrated approach with effective surveillance and management of kala azar fever in endemic region should be closely monitored (Sridhar, 2017; Rijal et al., 2019; Mubayi et al., 2010; Le Rutte et al., 2018; WHO/TDR, 2010). Kala-azar elimination programme is examined by the population based sero-surveillance and infection rates with effects were monitored (Sridhar, 2017; Olliaro et al., 2017; Rijal et al., 2019; Mann et al., 2021).

In general, prevention and control measures must be tailored to the local setting. Furthermore, leishmaniasis infected people are needed to maintain the cycle; this type of transmission (human—sand fly—human) is called anthroponotic. Therefore, in Bihar state of India, the transmission of *Leishmania donovani* is anthroponotic. In such areas, early detection and effective treatment of infected persons can serve as a control measure; suboptimal treatment can lead to development and spread of drug resistance (Sridhar, 2017; Olliaro et al., 2017; Rijal et al., 2019; Mann et al., 2021). Leishmaniasis is a complex clinical syndrome that is difficult to diagnose and treat. Advances in vaccine development, diagnosis, reporting, and treatment could prevent substantial morbidity and mortality from this disease (Mann et al., 2021). The immunotherapeutic and nanotechnology- based approach can further boost the drug discovery and development process for achieving therapeutic benefits (Gedda et al., 2020; Rahimi et al., 2020; Ray et al., 2021; Monteiro et al., 2019).

In another major development, DNA vaccines represented a promising approach for achieving protection against leishmaniasis (Maarouf and Abdlwahab, 2021). This study demonstrated the presence and expression of the ribosomal protein L5 gene in the Syrian strain of *Leishmania tropica* promastigotes (Maarouf and Abdlwahab, 2021). The sequence of the ribosomal protein cDNA L5 gene was determined and published in Genbank (Maarouf and Abdlwahab, 2021). The gene size was 918 bp. Expression was also demonstrated at the level of cDNA. This study also demonstrated that vaccination with the ribosomal protein L5 gene induces TH1 response in immunized mice (Maarouf and Abdlwahab, 2021). This response prevents the partial development of a skin lesion of Leishmania (Maarouf and Abdlwahab, 2021).

The leishmaniases are widely regarded as vaccine-preventable diseases based on disease natural history, epidemiological data (Duthie et al., 2017; Ashwin et al., 2021; Ismail et al., 2017; Zhang et al., 2020). Four vaccines for canine visceral leishmaniasis have reached the market (Ashwin et al., 2021). Artificial human infection ("leishmanization") with Leishmania had been practiced for centuries by people living in the Middle East and former Soviet states, where Cutaneous leishmaniasis (CL) is highly endemic (Ashwin et al., 2021). An adenoviral-vectored vaccine (ChAd63-KH) was found to be safe and immunogenic in healthy volunteers and in PKDL patients (Younnis et al. submitted) and is currently in Phase IIb as a therapeutic in Sudanese PKDL patients (Ashwin et al., 2021). Live genetically attenuated *L. donovani* centrin−/− parasite has shown efficacy in pre-clinical models and a *L. major* centrin−/− is soon to enter GMP production (Ashwin et al., 2021; Ismail et al., 2017; Zhang et al., 2020). An adjuvanted recombinant polyprotein vaccine (LEISH-F3/GLA-SE) has been progressed to Phase I and a newer derivative (LEISH-F3+/GLA-SE) evaluated in pre-clinical models (Duthie et al., 2017; Ashwin et al., 2021). RNA-based vaccines are also in development (Duthie et al., 2017; Ashwin et al., 2021; Zhang et al., 2020).

Cutaneous leishmaniasis (CL)

In Bihar state of India, 20% of the cured Kala-Azar patients developed post- Kala-Azar dermal leishmaniasis, which is chronic with disfigurement of cutaneous nodules is caused by *Leishmania donovani* (Adams et al., 2013; Rijal et al., 2019; Brindha et al., 2021; Karimi et al., 2021; Mann et al., 2021). Dermal leishmaniasis predominantly occured as localized Cutaneous leishmaniasis along with other aggressive forms like diffused Cutaneous leishmaniasis, mucosal leishmaniasis, and Cutaneous leishmaniasis (Mann et al., 2021). They cause several lesions/ disfigurement affecting the psychological well-being of the patients (Alvar et al., 2012; Croft and Olliaro, 2011; Rijal et al., 2019; Brindha et al., 2021; Mann et al., 2021). In general, Cutaneous leishmaniasis causes skin lesions, which can persist for months, sometimes years. The skin lesions usually developed within several weeks or months after the exposure but occasionally first appear years later (for example, in the context of trauma or immunosuppression) (Mann et al., 2021). Cutaneous leishmaniasis involves the development of large open sores/lesions from several small lumps at the site of insect bite that eventually heals on its own over an extended period of several months (Karimi et al., 2021; Mann et al., 2021; Matlashewski, 2001; Rijal et al., 2019; Brindha et al., 2021; Croft and Olliaro, 2011). Diffused Cutaneous leishmaniasis is another form of the disease where lesions are developed over a larger part of the body that resolves only with treatment (Karimi et al., 2021; Mann et al., 2021; Matlashewski, 2001; Rijal et al., 2019; Brindha et al., 2021). The leishmaniasis causative parasite showed many unique potential targets in the biochemical machinery. This includes some pathways or targets like the purine/pyrimidine salvage pathways nucleoside analogs, kinetoplastid proteasomes, mitochondria (Bora and Jha, 2020; Brindha et al., 2021; Croft and Olliaro, 2011; Mann et al., 2021), There are two major ways to identify compounds for these diseases: phenotypic and target-based approaches (Brindha et al., 2021).

Cutaneous leishmaniasis is globally increasing with significant female infections (2.35 million cases) (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017 Croft and Olliaro, 2011; Mann et al., 2021). Climatic conditions such as temperature, humidity and precipitation influences the vector borne diseases (Curtin and Aronson, 2021; Karimi et al., 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Leishmania vector sand flies require increased temperature for the development and survival. Thus, they may not tolerate freezing over winter (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). The top six burden countries with Cutaneous leishmaniasis cases were recorded in Guatemala, Syria, Iran, Cameroon, Iraq, and Tajikistan (Karimi et al., 2021; Scheufele et al., 2020; Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Furthermore, 70% of Cutaneous leishmaniasis cases were occurred in Afghanistan, Algeria, Brazil, Colombia, Costa Rica, Ethiopia, Palestine, Iran, Sudan, and the Syrian Arab Republic (Karimi et al., 2021; Maarouf and Abdlwahab, 2021; Torres-Guerrero et al., 2017; Mann et al., 2021). The high burden of Cutaneous leishmaniasis has been reported from Afghanistan, Palestine, Algeria, Colombia, Iran, Morocco, Pakistan, Peru, Saudi Arabia, Syrian Arab Republic, Tunisia, Brazil and Turkey (Karimi et al., 2021; Maarouf and Abdlwahab, 2021; Torres-Guerrero et al., 2017; Mann et al., 2021).

Cutaneous leishmaniasis in Syria is caused mainly by *Leishmania tropica*. It represents a serious health problem, which has aggravated further after the civil war in the country (Maarouf and Abdlwahab, 2021). *Leishmania major* is endemic in Israel and cases are often associated with travelers visiting areas of high transmission (Ashwin et al., 2021). An epidemiological study by Turkey confirmed the highest number of Cutaneous leishmaniasis in the refugees camps (Torres-Guerrero et al., 2017). In Mexico, the most characteristic form is the cutaneous-chondral form, also called “chiclero’s ulcer” which when affecting the ear cause the classic chiclero’s ulcer (gum tree harvester’s ulcer) (Torres-Guerrero et al., 2017). Leishmaniasis (Mundinia) *martiniquensis* in the Caribbean, *Leishmaniasis amazonensis* and *Leishmaniasis waltoni* as a cause of autocthonous Cutaneous leishmaniasis in the Dominican Republic, Guadelupe, Martinique, Grenada, and Trinidad and Tobago (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017).

Cutaneous leishmaniasis caused by *Leishmania mexicana* is endemic in some parts of US (Texas state) involving severe infections (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). The sand fly vector(s) of human leishmaniasis in the USA is not yet confirmed. The

recent deployment of American military to Iraq and Afghanistan has been associated with thousands of cases of Cutaneous leishmaniasis (CL) being recorded between 2002–2016 (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Since leishmaniasis is not a notifiable disease in the USA (except for Texas), it is difficult to assess the travel-acquired infection (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Another major concern is only 20% of the US population has been reported and 59% of the cases occurred in people with no travel history outside USA (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). However, the first case of diffuse Cutaneous leishmaniasis (DCL) was recorded in Texas, USA in 1903 followed by 80 autochthonous cases by 2020 (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Most autochthonous cases occured on exposed areas of the face, head, neck, or upper extremities, and affect both men and women of virtually any age (reported range from 2–89 years) (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Lesions are typically few in number, appearing as chronic, painless ulcers or papules usually about 1–2 cm size (Curtin and Aronson, 2021). *Leishmaniasis mexicana* lesions tend to heal in months, and in one study, 88% re-epithelialized in 14 weeks (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). Climate change, the identification of competent vectors and reservoirs, a highly mobile populace, significant population groups with proven exposure history, HIV, and widespread use of immunosuppressive medications and organ transplant all created the potential for increased frequency of leishmaniasis in the USA (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017). The blood transfusions/ tissue transplantation, inoculation, people immigration from global leishmaniasis endemic areas to the USA, shared equipment during intravenous drug use, and sand fly vectors were considered as the defined routes of transmission within the USA which resulted in reservoirs (Curtin and Aronson, 2021; McIlwee et al., 2018; Wright et al., 2008; Stahlman et al., 2017).

Mucocutaneous leishmaniasis (ML)

Mucosal leishmaniasis is caused by species in the *Viannia* subgenus particularly Leishmaniasis *[V.] braziliensis* but also Leishmaniasis *[V.] panamensis* and sometimes Leishmaniasis. *[V.] guyanensis*. Mucosal leishmaniasis is also caused by *L. (Leishmania) amazonensis*. Mucosal leishmaniasis is very rare in India, usually becomes clinically evident within several years (sometimes as long as decades) of the original cutaneous lesions, which typically were not treated at all. However, mucosal and skin lesions may be noted concomitantly (*Mucocutaneous leishmaniasis*), with cutaneous infection. Adequate systemic treatment of *Cutaneous leishmaniasis* caused by these species may reduce the risk for mucosal disease, but some risk may remain. Mucocutaneous leishmaniasis (ML) starts initially as Cutaneous leishmaniasis and later spreads to mucous membranes of pharynx, mouth, and nose, depletes the tissues, and causes excessive damage to the face, along with leprosy kind of stigma and impairment of breathing in critical cases (Brindha et al., 2021; Pal et al., 2017; Cruz et al., 2019; Mann et al., 2021). These patients were found to have a low quality of life with symptoms of depression, high anxiety, and low body image satisfaction (Brindha et al., 2021; Mann et al., 2021). The currently available anti-leishmanial drugs to treat leishmaniasis are associated with several side effects, toxicity, and drug resistance (Brindha et al., 2021; Mann et al., 2021). Mucocutaneous leishmaniasis leads to partial or total destruction of mucous membranes of the nose, mouth and throat. Over 90% of mucocutaneous leishmaniasis cases occur in Bolivia (the Plurinational State of), Brazil, Ethiopia and Peru (Ahmed et al., 2018; Mann et al., 2021;Brindha et al., 2021; Pal et al., 2017; Cruz et al., 2019). Mucosal leishmaniasis (also called *espundia*) traditionally refers to cutaneous infection, which results from dissemination of parasites from the skin to the naso-oropharyngeal mucosa (Brindha et al., 2021; Pal et al., 2017; Cruz et al., 2019; Mann et al., 2021). The magnitudes and determinants (parasite and host factors) of the risks for mucosal dissemination and for mucosal disease are poorly understood. The initial manifestations of mucosal leishmaniasis usually are persistent, unusual nasal symptoms (such as stuffiness or bleeding), although oral or pharyngeal symptoms sometimes were noticed first (Brindha et al., 2021; Pal et al., 2017; Cruz et al., 2019; Mann et al., 2021).

Herbal medicine treatment

A broad spectrum of medicinal plants was used as traditional remedies for various infectious diseases. Indian traditional herbal medicine is very famous since India is leading in the medicinal systems of Ayurveda

and Siddha (Malabadi and Nataraja, 2002a, 2002b; Malabadi, 2005, 2008; Malabadi et al., 2021a, 2021b, 2021c; 2021d, 2021e; Malabadi and Chalannavar, 2020; Malabadi and Vijayakumar, 2005, 2007 2008; Malabadi et al., 2005, 2007, 2009, 2010a, 2010b, 2011a, 2011b; Malabadi et al., 2012a, 2012b, 2012c, 2012d; Malabadi et al., 2016a, 2016b 2016c; Malabadi et al., 2017a, 2017b; Malabadi et al., 2018). Plants are the source of secondary metabolites present in the roots, stalks, leaves, fruits, seeds, vegetables, with a wide structural variety (Malabadi et al., 2021a, 2021b). Traditional herbs were consumed as main foods or teas, spices, and sauces. A considerable number of plant secondary metabolites have anti-protozoal activity (Gervazoni et al., 2020; Oryan, 2015; Schmidt et al., 2012a, 2012b; Randhawa et al., 2011; Mehwish et al., 2019). The alternative systems of herbal medicine have been used since ancient times and different extracts of medicinal plants and herbal formulations have demonstrated potential for use in Leishmaniasis such as plant lignans, neolignans, and Quinones, Alkaloids, Flavonoids, and Terpenoids (Maia et al., 2020; Gervazoni et al., 2020; Rodrigues et al., 2016; De Castro Oliveira et al., 2017; Saha et al., 2013; Chowdhury et al., 2012; Brito et al., 2019). Coumarins are derivatives that have a hydroxyl group, which differs in their biological properties. The diversity of structures within the coumarin group enables them to exhibit many biological activities, including anti-Leishmania activity (Oryan, 2015; Jain and Joshi, 2012; Gervazoni et al., 2020; Brezan et al., 2008, 2012; Tiuman et al.,2012; Ferreira et al., 2010; Silva et al.,2020). Carbohydrate derivatives, such as glycosides, starches, esters and sugar esters, caffeic acids are the most representative hydroxycinnamic acids were also tested against Leishmaniasis (Touaibia et al., 2012; Gervazoni et al., 2020).

The genus *Mimulus* is native to California in North America has also confirmed anti leishmania activity (Gervazoni et al., 2020). Ghosh et al., (2011) reported the root extracts and fractions of *Valeriana wallichii* showed anti leishmania activity (Ghosh et al., 2011). *Maclura tiinctoria* from the *Moraceae* family is a plant found in tropical countries worldwide, and its extracts are rich in flavonoids was also tested and showed anti-leishmania activity (Gervazoni et al., 2020). Plumbagin, a naphthoquinone extracted from *Pera benensis*, was tested against *Leishmania donovani* and exhibited an excellent IC50 value of 0.34 and 0.21μM for promastigotes and axenic amastigotes, respectively (Gervazoni et al., 2020; Sharma et al., 2012).

A series of 16 Brazilian medicinal plants were investigated in *in vitro* to determine their efficacy against *Leishmania amazonensis* (Gervazoni et al., 2020; Ribeiro et al., 2014). Among the 44 extracts and fractions, the most potent were the hexanic fraction of *Dipteryx alata* (D. alata) with an IC50 value of 0.08μg/mL (Ribeiro et al., 2014). The ethanolic fraction of *Hymenaea stignocarpa* with an IC50 value of 4.70 μg/mL and confirmed anti-leishmania activity (Gervazoni et al., 2020; Ribeiro et al., 2014). Both the chloroformic and ethanolic fractions of *Jacaranda cuspidifolia* (*J. cuspidifolia*), which exhibited IC50 values of 7.4 and 10.96μg/mL, respectively (Gervazoni et al., 2020; Ribeiro et al., 2014). Dyphylin, an arylnaphthalene lignin isolated from *Haplophyllum bucharicum*, is known to have activity against viruses, cancers and protozoa (Gervazoni et al., 2020).

In another study, Niranthin, a lignan from *Phyllanthus amarus*, was tested against *Leishmania donovani* (Chowdhury et al., 2012). The compound Niranthin was able to inhibit *Leishmania donovani* promastigote proliferation and exhibited good activity against intracellular amastigote with an IC50 value of 1.26μM (Chowdhury et al., 2012). The efficacy of a lignin found in garlic (*Allium sativum*) against *Leishmania amazonensis* promastigotes was investigated and showed anti- leishmania activity (Rodrigues et al., 2016). Four plants from different families, namely, *Asparagus gracilis* from the *Asparagaceae*, *Stellaria media* from the *Caryophyllaceae*, *Sida cordata* from the *Malvaceae*, and *Jurinea dolomiaea* (*J. dolomiaea*) from the *Asteraceae* family, were tested against a strain of *Leishmania tropica* isolated from a patient from Pakistan (Gervazoni et al., 2020; Shah et al., 2014). All four plants were prepared as methanol extracts or n-hexane, chloroform, ethyl acetate, n-butanol and water fractions. The most potent methanol extract was from *Jurinea dolomiaea*, which exhibited an IC50 value of 10.9μg/mL, but the highest anti-leishmanial activity was obtained from the ethyl acetate fraction from *Jurinea dolomiaea* with an IC50 value of 5.3μg/mL (Shah et al., 2014; Gervazoni et al., 2020). *Physalis angulata*, which is from the *Solanaceae* family, a well-known medicinal plant also tested against leishmaniasis (Mahalakshmi and Nidavani, 2014; Gervazoni et al., 2020). For leishmaniasis, Nogueira et al., (2013) tested the ethanolic extract of this plant against two species of Leishmania. In an anti-promastigote assay, the ethanolic extract of *Physalis angulata* exhibited IC50 values of 5.35 and 4.50 g/mL for *Leishmania amazonensis* and

Leishmania braziliensis, respectively. The antiamastigote assay using *Leishmania amazonensis* demonstrated an IC50 value of 1.23 g/mL (Nogueira et al., 2013; Gervazoni et al., 2020).

Saracoside and lyoniside, two lignan glycosides isolated from the medicinal plant, *Saraca indica*, were able to interact with L. donovani DNA, inducing apoptosis-like cell death (Saha et al., 2009, 2013; Gervazoni et al., 2020). Both doses of lyoniside and saracoside were capable of significantly decreasing the parasite loads in the spleen and liver (Saha et al., 2009, 2013; Gervazoni et al., 2020). *Plumarella delicatissima* is an octocoral specimen of the Southern Ocean known as a source of bioactive terpenoids. Seven terpenoids, (keikipukalide A-E, pukalide aldehyde, and ineleganolide) were isolated from *Plumarella* sp. and analyzed against *Leishmania donovani* amastigote. Pukalide aldehyde was the most promising compound, exhibiting an IC50 value of 1.9μM (Thomas et al., 2018; Gervazoni et al., 2020).

The potential activity of two biflavonoids isolated from *Selaginella sellowii*, amentoflavone and robustoflavone, was investigated against the intracellular amastigote of *Leishmania amazonensis* (Gervazoni et al., 2020). Brachydin A, brachydin B, and brachydin C, three dimeric flavonoids from *Arrabidaea brachypoda*, were evaluated against *Leishmania amazonensis*, *Leishmania braziliensis*, and *Leishmania infantum* promastigotes (Gervazoni et al., 2020). Several compounds isolated from leaves of *Piper rusbyi* were tested against three species of leishmania (Flores et al., 2007; Gervazoni et al., 2020). Among all the compounds tested, Flavokavain B, a chalcone, demonstrated good results against leishmania (Flores et al., 2007; Gervazoni et al., 2020). The IC50 value was 11.2μM against *Leishmania amazonensis*, *Leishmania donovani*, and *Leishmania braziliensis*, which was more effective than pentamidine (Flores et al., 2007; Gervazoni et al., 2020). Flavokavain B exhibited the best results among those tested, reducing the lesion size and being effective in vivo (Flores et al., 2007; Gervazoni et al., 2020).

In another study, *Helietta apiculata* Benth is a native plant of Paraguay, Brazil, and Argentina and is popularly known as "canela-deveado" in Brazil (Gervazoni et al., 2020; Ferreira et al., 2010). The (+)-3-(1′-dimethylallyl)-Decursinol and (-)- heliettin, two coumarins extracted from *Helietta apiculata* Benth, were tested against *Leishmania* amazonensis in vitro and in vivo (Gervazoni et al., 2020; Ferreira et al., 2010). In *Leishmania amazonensis* promastigotes, both coumarins were capable of decreasing parasite loads similar to those observed when the reference drug, meglumine antimoniate, was used (Gervazoni et al., 2020; Ferreira et al., 2010). The diversity of structures within the coumarin group enables them to exhibit many biological activities, including anti-leishmania activity (Gervazoni et al., 2020; Jain and Joshi, 2012). In another study, Mammaea A/BB, which was extracted from *Calophyllum brasiliense*, showed IC50 values of 7.4μM against promastigotes and 14.3μM against intracellular amastigotes of *Leishmania amazonensis* (Gervazoni et al., 2020; Brezan et al., 2008). Two coumarins obtained from stem bark of *Calophyllum brasiliense* demonstrated activity against amastigotes of *Leishmania infantum* (Gervazoni et al., 2020; Silva et al., 2020).

Tetradenia riparia, a plant from the *Lamiaceae* family, is commonly employed as a traditional medicine in Africa for infectious parasitic diseases, such as malaria, cryptococcosis, and candidiasis. This plant extracts were also tested against *Leishmania amazonensis* promastigote, and showed anti-leishmania activity (Gervazoni et al., 2020). Two neolignans, threo-manassantin A and erythro-manassantin A, isolated from *Saururus cernuus* exhibited activity against promastigotes (IC50 of 35.4 and 17.6 μM, respectively) and intracellular amastigotes (IC50 of 20.4 and 16.0μM, respectively) of *Leishmania amazonensis* (Gervazoni et al., 2020; Brito et al., 2019). Both molecules were determined to be able to interact with the parasite plasmatic membrane and to interfere with the parasite nucleus (Gervazoni et al., 2020; Brito et al., 2019). In another study, caffeic acid has leishmanicidal effects with a mechanism of action that triggers multiple targets that affect the viability of the parasite (Gervazoni et al., 2020; Bortoleti et al., 2019; Garcia et al., 2019).

Aspidosperma spruceanum Benth. ex Müll. Arg is a tree of the *Apocynaceae* family that has medicinal properties and has been used for leishmaniasis treatment in Amazonian regions (Morales-Jadán et al., 2020; Gervazoni et al., 2020). Combination therapy has been employed as a strategy for improving the treatment of leishmaniasis has been reported (Gervazoni et al., 2020). The combination of piperine and its analog capsaicin with meglumine antimoniate has been tested against *Leishmania* infantum. In this study, both alkaloids alone showed better antipromastigote activity

than meglumine antimoniate with IC50 values of 5.01µg/mL for capsaicin and 3.03 µg/mL (Gervazoni et al., 2020). The combinations of piperine or capsaicin with meglumine antimoniate (50% + 50%) were the most effective against promastigotes, exhibiting IC50 values of 2.1 and 2.9µg/mL, respectively (Gervazoni et al., 2020). Furthermore, piperidine alkaloids, such as (-)-cassine, (-)-spectaline, (-)-3- o-acetylcassine and (-)-3-O-acetylspectaline were extracted from a tree of *Senna spectabilis* (Fabaceae). These alkaloids were also tested against *Leishmania amazonensis* promastigotes, and all of them presented leishmanicidal effects, with compound (-)-spectaline being more effective (IC50 = 15.8µg/mL) (Lacerda et al., 2018; Gervazoni et al., 2020). Oleanolic acid and its isomer, ursolic acid (triterpenoids) were studied in promastigotes and intracellular amastigotes of *Leishmania amazonensis* (Gervazoni et al., 2020). Ursolic acid in promastigotes of *Leishmania* amazonensis induced programmed cell death independent of caspase 3/7 but dependent on mitochondria (Gervazoni et al., 2020). When the in vivo assay was performed for cutaneous leishmaniasis, the compound reduced the lesion size and parasite load (Yamamoto et al., 2015; Gervazoni et al., 2020).

Artemisinin extracted from *Artemisia annua* and its derivatives were tested against promastigotes of *Leishmania* major, demonstrating an IC50 value of 0.75µM (Sen et al., 2007, 2010; Gervazoni et al., 2020). Artemisinin was also evaluated against *Leishmania* donovani (Sen et al., 2007, 2010; Gervazoni et al., 2020). Further, against intracellular amastigotes, artemisinin presented an IC50 value of 3µM and was not toxic to the macrophages (Yang and Liew, 1993; Gervazoni et al., 2020). The IC50 value was 160µM against promastigotes and 22µM against intracellular amastigotes. Artemisinin induced apoptosis, depolarization of the mitochondrial membrane potential and DNA fragmentation. In vivo, using BALB/c mice infected with *Leishmania* donovani, artemisinin was administered at 5 and 10mg/kg/day to reduce the parasite burden in the spleen (Sen et al., 2007, 2010; Gervazoni et al., 2020).

Medicinal plants provide a first hand information for new drug discovery because of the presence of various chemical constituents and their ability to act on different biological targets (Malabadi et al., 2021a, 2021b; ; Malabadi et al., 2021a, 2021b). However, much work remains to be done to translate this potential into actual medicine. In rural areas, the home made crude plant extracts have been employed as medicinal drugs since the times of ancient civilizations. The traditional healers used the simple techniques of grinding the leaves of certain plants were considered to be medicine. The extracts from leaves, seeds, and other parts of the plant have been tested against several diseases, and some of these extracts have been highly successful in controlling highly infectious endemic diseases. Standardization of plant extracts is an urgent need in herbal drug research. Ayurvedic remedy is given in combination with milk to improve the immunity against many protozoan diseases. Herbal medicines are becoming popular due to their perceived effectiveness, safety and affordability. Scientific studies have started providing evidence and support for the use of herbal medicines aganist Leishmaniasis. Phytoconstituents responsible for pharmacological activities should be isolated, identified and systematically tested. Multicenter clinical trials should be performed to validate the efficacy of these herbal medicines alone or in the form of formulations for the treatment of leishmanial activity (Raj et al., 2020; Mehwish et al., 2019; Meena et al., 2010).

Some of the medicinal plant extracts with anti-leishmanial activity are, 1) Leaf extract of *Achillea millefolium*, and 2) *Chenopodium ambrosioides*, 3) the whole plant extract of *Tridax procumbens*, 4) The leaf extract of *Kalanchoe pinnata*, 5) *Allium sativum*, 6) the essential oil of *Chenopodium ambrosioides*, 7) the alcoholic extract of *Haplophyllum myrtifolium*, 8) leaf extract of *Aphelandra scabra*, 9) the bark tissue of *Byrsonima bucidaefolin*, 10) the bark of *Byrsonima carassifolin*, 11) leaf extract of *Clusia flava*, 12) bark extract of *Cupania deatata*, 13) the leaf of *Diphysa cartagenensis*, 14) whole plant extract of *Dorstenia contrajerva*, 15) *Jacaranda*, 16) *Warburgia ugandensis*, 17) the root extract of *Millerin quinqueflava*, 18) *Plumbago capensis*, 19) the root extract of *Vitex gaumeri*, 20) leaf juice of *Aloe vera*, 21) the whole plant of *Thymus vulgaris*, 22) *Hellieta aciculate*, 23) *Calluphyllum braziliensis*, 24) *Annona haematantha*, 25) *Colchicum kurdicum* (Bornm.) (Colchicaceae), 26) *Calophyllum brasiliense*, 27) *Tetradenia riparia*, 28) *Selaginella sellowii*, 29) *Arrabidaea brachypoda*, 30) *Mimulus bigelovii*, 31) Tunisian chamomile essential oil, 32) *Senna spectabilis*, 33) *Physalis angulata*, 34) *Pluchea carolinensis*, 35) *Aspidosperma spruceanum*, 36) The essential oil of *Cinnamomum camphora* for topical applications of Cutaneous leishmaniasis 37) Turmeric, *Curcuma longa* (*Zingiberaceae*), 38) Lemon balm (*Melissa officinalis*), 39) Eucalyptus oil

(Eucalyptus globulus) for topical applications in Cutaneous leshminiasis, 40) The essential oil of *Laurus nobilis* (Lauraceae) for topical applications of Cutaneous leishmaniasis, 41) Rosemary oil (*Rosmarinus officinalis* L.) (*Lamiaceae*) for topical applications of Cutaneous leishmaniasis, 42) Thyme oil (*Thymus vulgaris*) (*Lamiaceae*) for topical applications of Cutaneous leishmaniasis, 43) *Azidarachta indica* (Neem) (*Meliaceae*), 44) *Guduchi* or Giloy (*Tinospora cordifolia*) *(Amruthballi in* Kannada) (*Menispermaceae*), 45) Essential oil of *Tetradenia riparia* (Azadbakht et al., 2020; Dutta et al., 2007; Lakshmi et al., 2007; Lamidi et al., 2005; Mandal et al., 2006; Monzote et al., 2006, 2007, 2010; Peraza-Sánchez et al., 2007; Kigondu et al., 2009; Tempone et al., 2005; Ngure et al., 2009; Liebert, 2009; Singh et al., 2011; Ahmed et al., 1998; Ghosh et al., 2011; Iwu et al., 1992; Sawadogo et al., 2012; Brenzan et al., 2007, 2008, 2012; Demarchi et al., 2015; Rizk et al., 2014; Rocha et al., 2018; Salem et al., 2011; Hajaji, et al., 2018; Lacerda, et al., 2018; Mahalakshmi and Nidavani, 2014; Montrieux et al., 2014; Morales-Jadán et al., 2020; Muzitano et al., 2009; Malabadi et al., 2021a, 2021b; Demarchi et al., 2015; Meena et al., 2010).

Conclusions

This review paper has updated and summarized about the tropical neglected disease, leishmaniasis and herbal treatment as an alternative approach. A wide range of plant extracts exhibiting interesting antileishmanial properties *in vitro* and *in vivo* animal experimental studies were presented. This will encourage in the early drug discovery process for leishmaniasis (Kala azar) based on crude extracts, fractions, and isolated compounds obtained from natural products, specifically herbal-derived compounds. Natural products have been exploited by many research groups in India and throughout world for the novel and effective treatments to combat leishmaniasis. Although there are many possible drugs were used for the treatment of leishmaniasis. However, these drug-related treatments remain mostly ineffective, expensive, and long treatment, as well as causing side effects and leading to the development of resistance. Despite good knowledge on the epidemiology of leishmaniasis, it still remains uncontrollable and major public health issue in Bihar state, India. Therefore, there is an urgent need for the effectiveness of plant extracts, metabolites or formulations against different *Leishmania* species to clinical practice should be stressed to validate their activities.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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