REVIEW ARTICLE

Harnessing the Power of Curcumin: Evaluating Its Efficacy as an Antileishmanial Agent in the Fight Against Leishmaniasis

Minal Gopichand Ambilkar[1], Gaurav Sanjay Mude[2], Aashumi Ashok Kucheriya[3], Rahul Madhukar Bhoyar[4]

[1]*Department of Clinical Research Allied Health Science, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.*

[2]*Department of Pharmacology, Datta Meghe College of Pharmacy, Wardha Maharashtra, India.*

[3]*Department of Clinical Research Allied Health Science, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.*

[4]*Department of Pathology, Kasturba Gandhi Hospital, Wardha, Maharashtra, India.*

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ABSTRACT

Over 100 countries are impacted by the dangerous parasite disease leishmaniasis, which is categorized as a neglected tropical disease (NTD). Protozoan parasites use sandflies and other vectors to spread the disease. Herbal compounds like turmeric curcumin have demonstrated promise in the treatment of parasitic illnesses despite their limited bioavailability and water solubility. From small, self-healing skin lesions to serious intestinal infections, leishmaniasis can cause a wide range of illnesses in humans. Since there isn't a gold standard test for one type, mucocutaneous leishmaniasis (MCL), it can be difficult to diagnose. Treatments for MCL can be quite harmful, which emphasizes how crucial a correct diagnosis. This study aims to assess the diagnostic performance of PCR (polymerase chain reaction) for MCL and to compare the findings with the authors' most recent clinical research findings.

Keywords: Leishmaniasis, Curcumin, Antileishmanial, Protozoan parasites, Anti-inflammatory parasite.

Key Messages: In low-resource situations, curcumin shows significant promise as an inexpensive, natural medicine to treat leishmaniasis. Although its antileishmanial qualities, affordability, and safety are encouraging, more study is required to improve the dosage, formulation, and clinical efficacy.

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INTRODUCTION

Global public health is seriously threatened by leishmaniasis, a neglected tropical disease that is expanding quickly.It is brought on by several types of protozoan parasites known as *Leishmania*, which are spread via the sand fly bites from females.[1] A broad variety of protozoa in the genus *Leishmania* are responsible for the vector-borne illness leishmaniasis. There are three main ways it presents itself: cutaneous, mucocutaneous, and visceral.[2] Bright yellow chemical curcumin (CUR) is added to meals as an ingredient. The literature review has recently focused a lot of emphasis on CUR and the bioactive chemicals that are related to it. This systematic review aims to give an overview of CUR's antileishmanial properties and mechanism; potentially, the study's findings will lead to therapeutic and preventive applications.[3] Visceral, mucocutaneous, and cutaneous symptoms are the main manifestations of this illness, which presents an urgent risk because of the high rates of morbidity and mortality. Curcumin has several medicinal benefits, two of which are related to its anti-inflammatory and antioxidant qualities.[4] With or without the use of herbal extracts, electrospinning is a simple and effective technique for creating nanofibers of various diameters by using electric force to pull charged threads out of polymer solutions.[5] This work aimed to identify various bioactive compounds from the methanolic extract of C. longa rhizomes through a thorough phytochemical analysis, evaluate the extract's antioxidant potential through in-vitro testing using the DPPH free radical scavenging assay, and investigate the possible uses of curcumin as a natural antioxidant source in various industries.[6] The protozoan can be identified in both cutaneous or mucosal ulcers (particularly at the borders) and non-ulcerated lesions. Another diagnostic method that must be obtained at the active edge of the lesion is a biopsy with an amount from two to twenty in one cell, the smear can reveal

**Author for Correspondence: minalambilkar996@gmail.com*

parasites in free form, inside macrophages or, less often, in polymorphonuclear leukocytes Its dimensions are 2 to 5 µm in length and 1 to 2 µm in breadth, with an oval or pyriform shape with a rounded or oval nucleus.[7] Systemic therapy such as intramuscular or intravenous pentavalent antimonials, oral miltefosine, or intramuscular pentamidine isethionate, as well as topical medications such as paromomycin and intralesional application of pentavalent antimonials, are available for the treatment of CL.[8]

Types of Leishmaniasis

Mucocutaneous leishmaniasis (ML)

Mucocutaneous leishmaniasis, commonly called "espundia," is characterized by the pharyngeal and oral-nasal canals deteriorating, sometimes leading to abnormalities. Years after cutaneous leishmaniasis, it happens. The early signs and symptoms are merely minor nasal irritation and stuffiness, though ulceration and septal perforation may emerge gradually.[9] Figure 1 shows mucocutaneous leishmaniasis (MCL). A study has reported patient who developed ocular leishmaniasis as an uncommon side effect of long-term immunosuppressive therapy-induced multifocal MCL masquerades as an idiopathic midline granulomatous illness.[10] Leishmaniasis diagnosis is made more difficult by the fact that it can mimic both infectious and malignant disorders. For the same species, different endemic regions may respond differently to the same medication. Given that specific species of diseases have a higher probability of causing visceral involvement, knowing the species is very helpful in real-world situations.[11]

Visceral leishmaniasis (VL)

The protozoan *Leishmania donovani*, which belongs to the Kinetoplastida class, is the cause of visceral leishmaniasis (VL), commonly referred to as kala-azar. The disease known as VL, which can be lethal if untreated, is spread by phlebotomine sand flies it, is shown in Figure 2. Five nations account for 90% of the 500,000 yearly cases of VL: Sudan, Bangladesh, India, Nepal, and Brazil. 200 million people in more than 60 nations are impacted by VL.by 2015, the World Health Organization (WHO) hoped to abolish tropical diseases that are often ignored, such as VL.[12]

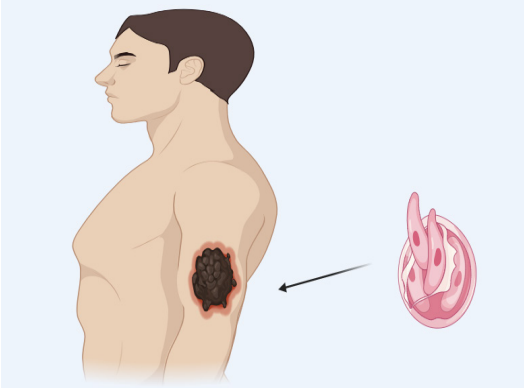

Figure 1: Mucocutaneous leishmaniasis

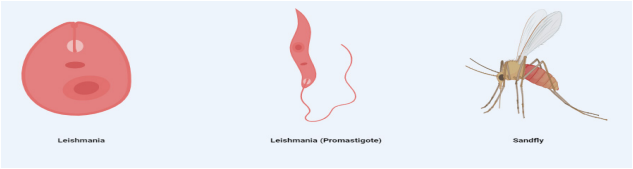

Figure 2: Visceral leishmaniasis

Cutaneous leishmaniasis

There are several clinical symptoms associated with leishmaniasis, the most prevalent of which is cutaneous leishmaniasis. The disease's epidemiology and clinical features vary greatly because of the interactions between various parasites, hosts, vectors, and environmental factors. Figure 3 shows microscopic picture of Leishmania.[13] Leishmaniasis is a disease caused by a genus of protozoan parasites, and the main carriers of the disease are sandflies, especially female Phlebotomus and Lutzomyia species. Leishmaniasis has been identified by the World Health Organization (WHO) as a neglected tropical disease (NTD), highlighting the illness's substantial effects on public health and society, particularly among low-income populations.[14] One of the biggest global health issues, leishmaniasis, is becoming more common. Travelers returning from endemic areas are observed to exhibit it in Northern Europe. Sandflies carry the protozoa, which can cause anything from a minor ulcer to a deadly systemic illness. *Leishmania braziliensis* lesions have the potential to develop into "espundia," a mucocutaneous variant, and should be treated with systemic antimony.[15]

Drugs for leishmaniasis treatment

The conventional therapy for pentavalent antimony (Sb5+) has long been in place. Pentamidine, on the other hand, was taken off the market due to growing toxicity and resistance, while amphotericin B, although effective, can be extremely costly and necessitate hospitalization. Multiple medication combination therapy has demonstrated superior efficacy, resulting in reduced adverse effects and shortened treatment durations. Drug resistance has also been brought on by incorrect drug use. We shall go into further depth about the many kinds of these drugs.[16] These symptoms are frequently linked to the host's immunological state. Studies on the mechanisms of action of medications used to treat leishmaniasis are scarce. Previous research has demonstrated that sodium stibogluconate [Sb(V)] inhibits amastigotes from generating macromolecules.[17]

Pentavalent antimony (Sb 5+)

Under certain conditions, sodium stibogluconate and meglumine antimoniate (MA), two pentavalent antimony medicines, have demonstrated considerable promise in treating both cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL). For the treatment of CL, the WHO advises utilizing both intralesional and systemic antimonials. Because intralesional injection permits high local concentrations of the medicine with few systemic side effects, it is especially advantageous for treating isolated CL lesions. The World Health Organization

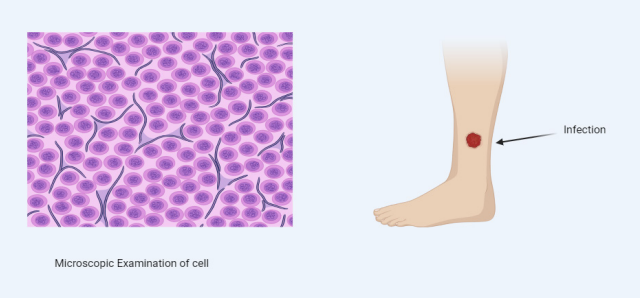

Figure 3: Cutaneous leishmaniasis

recommends treating the lesion by injecting 1-3 cc of pentavalent antimony solution under it until the skin is pale.[18]

Amphotericin B

Visceral leishmaniasis (VL) is treated with specific anti-leishmanial drugs in conjunction with strict control of any coexisting infections, anemia, and malnourishment. In many areas, pentavalent antimonials have long been the recommended treatment for viral load. As previously stated, studies have shown that cholesterol in the host membrane is essential for *Leishmania* promastigotes to adhere to and infiltrate macrophages.[19] Cholesterol from membranes has been removed with the application of methyl-β-cyclodextrin (MβCD). When macrophages are treated *in-vitro* with MβCD, membrane cholesterol is eliminated, which decreases *Leishmania* promastigotes' ability to bind and infect them. Since prehistoric times, people have mostly derived their therapeutic ingredients from plants. Throughout history, they have had a significant impact on economic, intellectual, and cultural pursuitsm.[20]

Ambisome (Liposomal Amphotericin B)

Ambisome (liposomal amphotericin B) is a tiny molecule that has the ability to efficiently infiltrate tissues and circulate in the body for a prolonged duration. They are spherical vesicles with lipid bilayers encircling an aqua core, and they show incredible pharmacokinetic effects. Moreover, the goal of liposomes is to maximize antifungal activity while reducing drug toxicity. AmB's liposome architecture and improved stability may make it possible for the active ingredient to more successfully engage bacteria at several infection sites.[21]

Vaccine against leishmaniasis

The most economical method of preventing infectious diseases is vaccination. There are various types of vaccinations that fall under this category: DNA vaccines, subunit vaccines, lethal vaccines, attenuated vaccines, virus-like particle (VLP) vaccines, and recombinant vaccines. Immunological reactions triggered by preventative vaccinations improve memory cell production, which is essential for managing illnesses. Moreover, vaccinations support humoral and cellular immunity, especially cytotoxic cells and a strong Th1 response, both of which are critical for eliminating infections.[22]

First-generation vaccines

Prophylaxis

One of the ingredients in first-generation leishmaniasis vaccines is whole-killed parasites. These vaccinations might be made in underdeveloped nations for extremely little money. Interest in vaccine development has increased as a result of this benefit. Human clinical trials have recently examined three distinct kinds of first-generation vaccines using *L. major, L. amazonensis*, and *L. mexicana*.[23] Sandflies are the primary vector of canine leishmaniosis (CanL), a serious zoonosis that can possibly kill both people and canines. Worldwide, there are infections brought on by various *Leishmania* species in a range of geographical locations with diverse climatic circumstances. Human leishmania infection has been classified into three types based on clinical manifestations: cutaneous, mucocutaneous, and visceral.[24]

Second- Generation vaccine

Live vaccinations

This group comprises genetically engineered vaccinations that lack vital genes such as biopterin transporter, dihydrofolate reductase, cysteine proteinase, and/or thymidylate synthase. These altered parasites have the ability to successfully trigger adaptive immune reactions, which inactivate the infection and render vaccinated persons healthy. The *Leishmania* genome also uses suicide cassettes as a tactic. Nonetheless, a number of studies indicate that long-term immunity against leishmaniasis may result from immune responses against live infections that carry distinct antigens.[25]

Vaccines based on purified Leishmania antigens

Leishmania's ability to get past immune barriers is essential to its survival within its mammalian host. Due to its intracellular nature, *Leishmania* directly eludes humoral immune responses, but it also makes itself vulnerable to cell-mediated immunity. As part of its subversive activity, *Leishmania* upregulates nitric oxide (NO), IFN-γ, and inducible nitric oxide synthase (iNOS). Additional second-generation vaccines exist in the form of isolated *Leishmania* sub-fractions, which may contain the parasite's proteins or lipophosphoglycan.[26]

Third-generation vaccination

Their dissemination doesn't necessitate a cold chain, and they can effectively blend several genes into one product. DNA vaccines function by promoting innate immunity, which sets off future immune reactions. This happens via the nonmethylated CpG sequences that are commonly present in the DNA of bacteria. It is possible to produce recombinant proteins with a prolonged half-life and native shape by use of robust host cell replication.[27]

Origins of curcumin

Natural plant products have been used for many different reasons throughout human history. Numerous plants that naturally produce these compounds have coevolved with mammalian life over billions of years. Numerous natural substances have biological or pharmacological qualities that can be applied to the development and discovery of new

pharmaceutical drugs.[28] The phytochemical curcumin, which has anticancer properties, was isolated from the rhizomes of *Curcuma longa* L. It's likely that curcumin is more toxic to tumor cells in particular and less dangerous to healthy ones. Similarly, curcumin can particularly change how cytotoxic a variety of chemotherapy medications are to tumor cells.[29]

Medical interventions of curcumin

Chronic inflammation is a major factor in diseases associated with lifestyle choices, including obesity and poor glucose tolerance, as well as cardiovascular disorders. A naturally occurring substance called curcumin has been demonstrated to offer several physiological benefits in addition to anti-inflammatory qualities. On the other hand, curcumin is seldom bioavailable in humans. It is anticipated that over time, more data will become available about the clinical use of curcumin in disorders linked to a chronic inflammatory lifestyle.[30]

Curcumin as a traditional medicine

For millennia, traditional medicines from all around the world have used turmeric. Turmeric is thought to provide several health advantages in Ayurvedic traditions. It is claimed to cure arthritis, ease gallstones, reduce gas, get rid of worms, enhance digestion, control menstruation, and promote general energy. Turmeric is used as an antibacterial and antiseptic in South Asian countries to heal burns, wounds, and bruises. As a cholagogue, it helps the body digest fats better by promoting the production of bile in the liver and its expulsion through the gallbladder.[31]

Antileishmanial activity in-vivo studies

Antileishmanial activity *in-vivo* investigations have demonstrated encouraging outcomes with a variety of substances. With IC_{50} values similar to those of the common medication miltefosine, fisetin, 3-hydroxyflavone, and luteolin demonstrated strong antileishmanial action. Quercetin also showed some *in-vivo* effect, suppressing the infection by 15.3%. In mouse studies, mahanine exhibited strong antileishmanial action, causing nearly total parasite clearance and boosting immunological responses. These results demonstrate the variety of sources for substances having antileishmanial characteristics.[32]

Mechanism involved in curcumin

Throughout history, functional foods have been utilized for medical purposes. Growing interest has been seen in studies on dietary supplements and functional foods for a range of illnesses in the last few decades. One of the most researched functional foods is turmeric, sometimes referred to as *C. longa* L. or *C. domestica* Valeton. Turmeric is a member of the Zingiberaceae family and is mostly grown in Asia's tropical regions. It is also known as turmeric root or yellow root. The plant has funnel-shaped, yellowish blooms and oblong leaves, usually reaching a height of 3 to 5 feet. Well-drained sandy or clay loam soils with a pH of 4.5 to 7.5 and a high organic matter content are ideal for the growth of turmeric.[33]

Anti-inflammatory effects of curcumin

The skin is a vital organ that is involved in numerous bodily functions. It functions as a thermal regulator, a sensory receptor, an excretory and secretory organ, and a protective layer. Furthermore, it actively participates in a variety of metabolic activities. The body's internal organ functions and overall health can be externalized through the skin. Skin alterations occur in conjunction with other illnesses or as a side effect of medicine. They may also result from a fungal, bacterial, or viral infection or from a contact allergy. Plant-based treatments are an effective treatment for many skin conditions.[34] The four parts of the inflammatory process are effectors, sensors, mediators, and inducers. There is still a great deal of confusion around the distinct physiological and pathological pathways of inflammation brought on by different inflammatory triggers. Generally speaking, drugs that have anti-inflammatory properties work by blocking a medium's influence on a target tissue, producing mediators that counteract inflammation, controlling how target tissues react to inflammatory mediators, and influencing receptors and signaling pathways. By preventing the synthesis of pro-inflammatory mediators and altering pro-inflammatory signaling pathways, curcumin lowers inflammation and interacts with peroxisome proliferator-activated receptor gamma (PPARγ) to suppress NF-κB. Clinical trials, animal studies, and experimental/research findings are linked to the inflammatory process of the aforementioned disorders in this review.[35]

Immunomodulation

A spherical, non-motile amastigote that differs from promastigotes both morphologically and biochemically is the form that *Leishmania* takes during its simple two-stage life cycle: the intracellular phase and the life stage, when the parasite multiplies inside phagolysosomes found in virtual cells.[36] Numerous *in-vitro* and *in-vivo* studies have been conducted to investigate the wide range of biological and pharmacological activities of the bioactive compounds present in turmeric species. These activities include antioxidant, anti-inflammatory, anticancer, hepatoprotective, antifungal, antihypertensive, neuroprotective, and immunomodulatory effects. The bioactive substances found in six species of turmeric are the main subject of this article. Comprehensive mechanistic evaluations of the immunomodulatory impacts of several species are available in the literature. It offers a comprehensive analysis of the impacts of various plant extracts on the immune system in addition to a synopsis of their fundamental mechanisms of action.[37]

Antioxidant properties curcumin

Curcumin, the active component of turmeric, and its fat- and water-soluble derivatives have powerful antioxidant properties that are comparable to those of vitamins C and E. Ischemia research has shown that pretreatment with curcumin reduced changes in the heart caused by ischemia. Curcumin has been shown to inhibit cyclosporin A-resistant phorbol myristate-acetate + anti-CD28-associated T-cell proliferation pathway. In

addition, curcumin decreases malondialdehyde (MDA) levels and increases glutathione (GSH), testosterone, and glucose-6-phosphate dehydrogenase (G6PD) to reduce testicular damage caused by exposure to di-n-butyl phthalate (DBP).[38]

CONCLUSION

In conclusion, curcumin has significant potential as a natural and affordable therapeutic agent for leishmaniasis, potentially filling the critical need for new medicines against this neglected tropical illness. Especially in settings with low resources where the disease burden is greatest, its incorporation into standard clinical practice could make a major contribution to worldwide efforts to manage and eradicate leishmaniasis. The study highlights curcumin's powerful antileishmanial properties and demonstrates how well it works to treat leishmaniasis. Due to its diverse modes of action, which include regulating host immune responses and preventing parasite growth, curcumin is a highly promising therapy option for leishmaniasis. A number of investigations has clarified curcumin's capacity to interfere with important cellular functions in Leishmania parasites. These understandings of its mechanism of action offer a strong basis for additional research and development of curcumin-based treatments for leishmaniasis Curcumin, it is significant, has a positive safety profile that suggests that it may be used as a leishmaniasis treatment. Its high degree of tolerance allays worries about side effects that are frequently connected to prescription drugs. Even though curcumin exhibits potential, issues with pharmacokinetics and bioavailability must be resolved before it can be successfully used in clinical settings. To optimize curcumin's therapeutic efficacy, more research must be done to improve the drug's formulation and distribution. The results highlight the necessity of additional investigation to maximize curcumin-based therapies for the treatment of leishmaniasis.

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