Original Article

Effect of Curcumin on the Dissemination of *Leishmania major* in Different Organs of infected BALB/c Mice Using Quantitative PCR Method

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ABSTRACT

Background: Leishmaniasis is considered as a significant public health concern globally. It ranks as the second most prevalent parasitic disease following malaria. The side effects of the drugs used in the treatment of leishmaniasis and the development of resistance against these drugs have caused many researchers to find an alternative treatment method. The most effective methods in the treatment of protozoan parasitic infections, such as leishmaniasis, can be natural plant products.

Objectives: This study aimed to investigate the effects of curcumin on the dissemination of leishmaniasis in different organs of mice.

Methods: Mice were experimentally infected with *Leishmania major* and placed in 6 groups. The control groups, the group treated with glucantime as the standard method, and the group treated with curcumin at 40, 80, and 120 µM. The livers, spleens, hearts, lungs, and kidneys of these mice were collected, and parasite dissemination in the tissues was investigated using quantitative polymerase chain reaction (PCR). The intensity of the parasite-derived PCR product was divided by the intensity of the mouse genome-derived PCR product, which was used as a marker for parasite burden in the organs, and the data were analyzed using SPSS.

Results: *Leishmania major* amastigote bands were not detected in the heart, kidney, and lung tissues of any group by quantitative PCR. However, *Leishmania* bands were observed in the liver and spleen of the control groups. Notably, the parasite band was absent in the spleen of mice treated with curcumin and glucantime. Furthermore, the infection burden in the liver of mice receiving curcumin and glucantime treatment was comparable to the untreated control group.

Conclusion: The quantitative PCR analysis of DNA extracted from the liver showed no significant differences in parasite burden in comparison with control groups. Treatment with glucantime and curcumin prevented the spread of *Leishmania* to the spleen.

Keywords: Curcumin, *Leishmania major*, Organ dissemination, Quantitative polymerase chain reaction (PCR)

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Introduction

Leishmaniasis, caused by the eukaryotic parasite *Leishmania*, remains a significant health challenge in tropical and subtropical countries worldwide, including Iran, Iraq, Pakistan (Ahmed et al., 2019) and Afghanistan (Lange et al., 2024). The disease manifests in various forms, ranging from cutaneous leishmaniasis (CL) to the visceral leishmaniasis (VL), and mucocutaneous leishmaniasis (MCL). *Leishmania major* is one of the main causative agents of CL, widespread in parts of the Middle East, Africa, and Central Asia (Kaye & Scott, 2011). Given the limited availability of effective vaccine candidates, drug therapies currently represent the only option for managing CL. Bavarsad Ahmadpour et al. (2022) described a possible vaccine based on multiple peptides derived from LACK, LeIF, GP63, SMT antigens of *L. major.* The primary treatment options for leishmaniasis include sodium stibogluconate (SSG), meglumine antimonate (glucantime), amphotericin B, miltefosine, and paromomycin (Alemu et al., 2023). However, the efficacy of these medications is increasingly compromised by adverse side effects and the emergence of drug resistance, particularly in endemic regions where the prevalence of the disease is significant. Consequently, it is essential to explore novel natural compounds with anti-leishmanial properties for the development of advanced pharmaceuticals (Dourado et al., 2024).

As reported by the World Health Organization (WHO), approximately 80% of the global population utilizes herbal compounds to treat various diseases. Recently, there has been a growing interest in natural products, especially herbal compounds, as promising alternatives or complementary therapies for addressing various parasitic diseases, including leishmaniasis (Amini et al., 2023; Taheri et al., 2024). Curcumin, a polyphenolic compound extracted from the rhizome of *Curcuma longa*, has been considered a promising option due to its diverse therapeutical properties. It is generally known for its anti-inflammatory, antioxidant, and immunomodulatory effects, which have been thoroughly investigated in relation to various infectious diseases (Shirmohammad et al., 2024). The exact mechanism through which curcumin exerts its antileishmanial effects is not yet fully uncovered. However, recent studies indicate that curcumin may disrupt the parasite's ability to survive and reproduce within host macrophages. Curcumin displays antioxidant properties that may decrease oxidative stress in infected tissues, thereby improving the host's immune response to the infection (Sahebi et al., 2024). Furthermore, curcumin may influence the expression of numerous pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are critical in the immune response to leishmaniasis (Alinejad et al., 2022; Zhong et al., 2020). Given these diverse effects, curcumin presents a promising opportunity for further exploration in treating leishmaniasis.

Although there is increasing evidence indicating the potential benefits of curcumin in the management of parasitic infections, its role in the dissemination of *L. major* in different organs has not been extensively investigated. The current study aimed to investigate the impact of curcumin on the dissemination of *L. major* in various organs, specifically the liver, spleen, lungs, and kidneys, of BALB/c mice that have been infected with *L. major*. This study used a well-established mouse model of leishmaniasis to assess the parasitic load in these organs after administering curcumin at various concentrations. It also compared the effectiveness of curcumin to that of glucantime, the conventional treatment for leishmaniasis.

Materials and Methods

Ethical statement

The presented study was approved by the Ethical Committee of the Faculty of Veterinary Medicine, University of Tehran.

Sample preparation

Iran's standard strain *L. major* (MRHO / IR / 75 / ER) was obtained from the Department of Parasitology of Tehran University of Medical Sciences and prepared as described by Shirmohammad et al. (2024).

Preparation of nanocurcumin

Nanocurcumin was prepared by dissolving 95% of curcumin in dimethylsulfoxide (DMSO) at different concentrations (40, 80, and 120 µM). Their stability was assessed by High-performance liquid chromatography (HPLC), and the size and zeta potential of the particles were measured by Day Petronic Company (Zetasizer Nano-ZS) as described by Shirmohammad et al. (2024).

Infection of mice with *L. major* (MRHO/IR/757ER)

Sixty BALB/c mice (4–6 weeks old, weighing about 20–25 gr, purchased from the Faculty of Veterinary Medicine, University of Tehran) were divided into six groups: control I (no treatment), control II (liposome without curcumin), positive control (treated with glu-

Table 1. Concentration of the PCR product of the P to the H concentration for samples from the mice experimentally infected with Leishmania and treated with different curcumin concentrations and glucantime

Treatment	Mean±SE		
	Liver	Spleen	Skin
Control 1	0.72±0.11	0.17±0.23	0.84±0.07
Control 2	0.37±0.03	0.38±0.1	1.3±0.16
C40	0.52±0.39	0	0.37±0.16
C80	0.41±0.08	0	0.38±0.06
C120	0.43±0.08	0	0.42±0.13
Glucantime	0.39±0.05	0	0.34±0.12

Note: Control 1: Without any treatment; Control 2: Treated with nano-liposome without curcumin; C40: Treated with curcumin at 40 µM; C80: Treated with curcumin at 80 µM ; C120: Treated with curcumin at 120 µM.

cantime), and three test groups treated with nanoliposomal curcumin at concentrations of 40, 80, and 120 µM. Mice were housed in standard laboratory conditions (controlled temperature 21±1 ˚C and relative humidity 50±5%).

For infection, promastigotes were first cultured and then used for subcutaneous infection of the mice as previously described by Shirmohammad et al. (2024). Following lesion development, the mice were treated subcutaneously with 40 µM (group 1), 80 µM (group 2), and 120 µM (group 3) nanoliposomal curcumin once every two days. As positive control (group 4), the mice were treated with 20 mg/kg glucantime, and as negative controls (groups 5 and 6), the mice were untreated or treated with liposome without curcumin.

Sample preparation and DNA extraction

Genomic DNA was extracted from skin lesion as described by Shirmohammad et al. (2024) and from the liver, kidney, heart and spleen of infected mice using the MBST kit (Tehran, Iran) according to the manufacturer's instructions.

Quantitative PCR

The amplification of the extracted DNA was performed using specific common primers for *Leishmania* spp. and mice designed from the *18S rRNA* genes of the respective species, yielding PCR products of 255 bp for DNA originating from mice and 360 bp for DNA originating from *Leishmania* spp. The sequences of the forward and reverse primers are as follows: (5′AGAGGTGAAATTCTTGGACCG-3′) and (5′ TTCCGTCAATTCCTTTAAGTTTCA-3′). Amplification reactions were prepared in a total volume of 25 µL, containing 12.5 µL of Taq PCR Master Mix (Master Mix RED, SinaClon, Iran), 1 µL of each primer (10 pmol), and 1 µL DNA template. The PCR conditions were: initial denaturation of DNA strands at 95 ˚C for 5 min followed by 35 cycles of denaturation at 94 ˚C for 45 s, annealing at 53 ˚C for 45 s, and extension at 72 ˚C for 45 s, followed by a final extension at 72 ˚C for 10 min. PCR products were analyzed by 2% agarose gel electrophoresis using SYBR Safe gel stain (Thermo Fisher Scientific, USA) or ethidium bromide.

Statistical analysis

The intensity of the PCR product derived from the parasite and from mouse genomic DNA was determined using GelQuant.NET version 1.8.2. Subsequently, the quantity achieved from the parasite was divided by the intensity of the PCR product derived from mouse genome. The resulted index was used as a marker for parasite burden in the organs (Shirmohammad et al., 2024). The statistical analysis was performed by the nonparametric Kruskal-Wallis test ($P<0.05$) using SPSS software, version 26 (IBM).

Results

The DNA extracted from the skin, liver, kidney, and spleen was amplified using common primers derived from the *18S rRNA* gene of the parasite and from the host genome. These primer pairs can simultaneously amplify the corresponding region of the *18S rRNA* gene from the parasite, as well as from host *18S rRNA* gene. This means that with a single PCR, it is possible to quantitatively analyze the parasite burden in certain samples

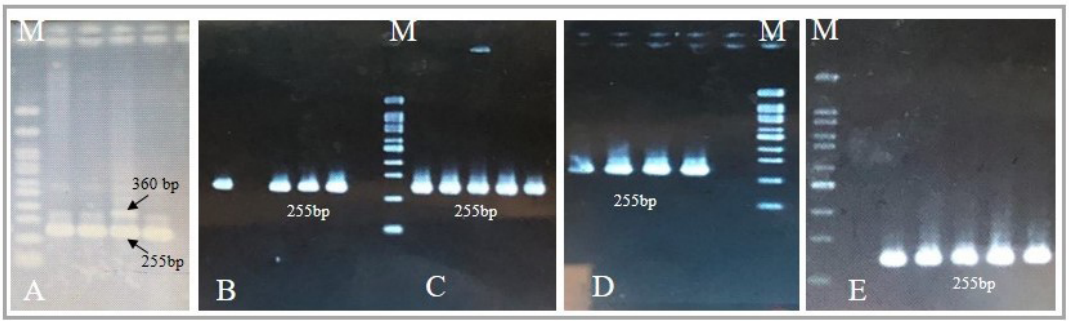

Figure 1. DNA was extracted from spleen of mice experimentally challenged with *L. major* and from untreated and treated groups with different concentrations of curcumin and glucantime

Note: The PCR product derived from host DNA is 255 bp and from parasite is 360 bp. M: 100 bp DNA marker; A: Untreated group, B: Treated with curcumin at 40 µM; C: Treated with curcumin at 80 µM; D: Treated with curcumin at 120 µM; E: Treated with glucantime.

originating from different organs. The ratio between the intensity of the PCR product from the parasite (P) to the intensity of the PCR product from the host (H) gives the P/H index for estimating parasite burden. Quantitative PCR analysis of the infected skin region showed that the parasite burden was significantly lower in infected mice treated with different concentrations of curcumin, as well as glucantime in comparison to both control groups. The Kruskal-Wallis test on the skin of infected mice showed a statistically significant difference in the mean P/H index among treatment groups (χ^2 (4)=13.2, P=0.01). Post hoc tests showed that 40 µM and 120 µM concentrations of curcumin significantly reduced the index compared with control II (P=0.03), while 80 µM curcumin produced a significantly lower index than both control I (P=0.04) and control II (P=0.02) (Table 1).

Notably, quantitative PCR analysis of the DNA extracted from the spleen of the above-mentioned mice showed detectable parasite burden only in mice in the control groups compared with treated mice with curcumin (40, 80, and 120 µM) and glucantime (Figure 1).

Kruskal-Wallis test for the spleen results also showed a statistically significant difference in the mean P/H index between treated and control groups (χ^2(5)=25.39, P<0.001) (Table 1). Post-hoc Dunn's pairwise test for groups showed that the groups treated with 40 µM, 80 µM, 120 µM curcumin and glucantime significantly reduced the P/H index compared with groups C1 and C2 (P<0.001) (Figure 2).

Kruskal-Wallis test for the liver showed no statistically significant differences in the mean P/H index among treatment groups (P>0.05) (Figure 2, Table 1).

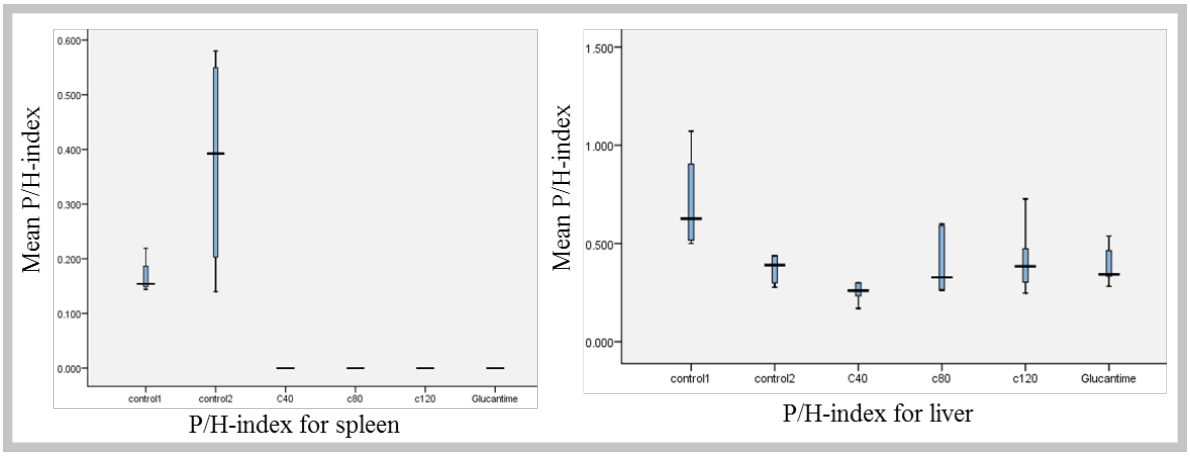

Figure 2. Intensity of the PCR product of the P to the H for samples (P/H-index) from the spleen (left) and liver (right) of the mice experimentally infected with *Leishmania* and treated with different curcumin concentrations and glucantime

Note: Control 1: No treatment; Control 2: Treated with nano-liposome without curcumin).

In comparing data from the heart, lungs, and kidneys, no statistically significant differences were observed in these organs, and no parasites were detectable in any of these samples.

Discussion

L. major is the causative agent of zoonotic CL. It has been reported that experimental infection of BALB/c mice with *L. major* promastigotes resulted in the spread of the parasite to the liver, spleen, and bone marrow (Nasseri & Modabber, 1979). firmed the dissemination of *L. major* in a mouse model Makwali et al. (2012) also con. Also, *L. major* amastigotes were detected in different organs of trapped urban mice (Shahabi et al., 2023). Therefore, it is important to investigate the parasite dissemination not only in the skin lesion region but also in other organs, like the liver and spleen in the experimental Leishmania- infected mice treated with drug candidates.

Antileishmania therapy is associated with several problems, including severe side effects. One of the most used therapeutic agents is a drug based on pentavalent antimony (glucantime). Meglumine antimoniate (glucantime) is an antimonial compound characterized by the molecular formula C7H18NO8Sb. It is synthesized through the reaction of pentavalent antimony (SbV) with N-methyl-D-glucamine, a derivative of carbohydrates. This compound is the primary choice for the treatment of leishmaniasis (Pourmohammadi et al., 2011; Roberts et al., 1998). Glucantime functions by influencing the bioenergetic pathways of the amastigote stage of *Leishmania*, leading to the disruption of oxidation and glycolysis processes. This action results in a decrease in cellular levels of adenosine triphosphate (Moreira et al., 2017). Given the clinical adverse effects associated with glucantime and its impact on various organs, it is essential to combine it with compounds that exhibit fewer side effects in order to enhance its efficacy (Yadegari et al., 2023; Oliveira et al., 2011) or to replace it with drugs with fewer side effects.

Recent investigations have focused on the potential application of herbal compounds in the treatment of *Leishmania* infections. Among these, curcumin has emerged as a particularly effective herbal agent. Curcumin, which is recognized as a natural product approved by the FDA, demonstrates a wide range of pharmacological activities (Dai et al., 2020), including anti-cancer (Shakibaei et al., 2013), anti-inflammatory (Buhrmann et al., 2021), antioxidant (Laali et al., 2020), anti-mutagenic, wound-healing antibacterial (Chopra et al., 2021), and antiprotozoal effects (Aqeele et al., 2019; Aqeele et al., 2021; Shirmohammad et al., 2024). Anti protozoal properties of curcumin have been demonstrated for *Plasmodium falciparum* (Cui et al., 2007; Ekawardhani & Berbudi, 2020), *Leishmania donovani* (Das et al., 2008; Albalawi et al., 2021), *Trypanosoma* (Nose et al., 1998; Novaes et al., 2016; Jonah & Enoh, 2020), and *Giardia lamblia* (Ranjbar et al., 2021). A study demonstrated that curcumin administration in mice infected with *Plasmodium berghei* resulted in a reduction of blood parasitemia by 80–90% and significantly improved survival rates in the affected mice (Reddy et al., 2005). The anti-proliferative impact of curcumin has been considered against three *Leishmania* species (*L. major*, *L. tropica* and *L. infantum*). The leishmaniacidal effects of curcumin compared with pentamidine, clearly show that curcumin has a higher effectiveness in vitro (Elamin et al., 2021; Saleheen et al., 2002). Another study assessed the effect of curcumin on promastigotes of *L. major* for 12 h and 24 h in vitro. Also, the morphology of the flagellum and cell shape changed in a concentration- and time-dependent manner, which was determined by MTT and Trypan blue assays (Aqeele et al., 2019). A study also showed the positive effect of curcumin on *L. major* amastigotes in vitro (Aqeele et al., 2021). Curcumin exhibited effects similar to those observed in the group treated with glucantime in mice experimentally infected with *L. major* (Shirmohammad et al., 2024). It was important to investigate the effect of curcumin on the dissemination of the parasite within the control, curcumin-, and glucantime-treated experimental infected mice groups. In the present study, it was shown that the parasite spread to the liver occurred in all mice, with no significant decrease in the curcumin- and glucantime-treated groups compared to control groups.

Interestingly, in contrast to mice treated with curcumin or glucantime, parasite dissemination was detected in the spleens of control-group mice. No dissemination of parasites was detected by qPCR in the kidneys, heart, or lungs in any of the examined groups.

Conclusion

In conclusion, the findings of this research provide strong evidence supporting the potential of curcumin as an alternative or adjunct topical treatment for CL. Since treatment with curcumin had the same therapeutic effect on skin lesions as glucantime, and given the high toxicity and severe side effects of glucantime, it is recommended to consider using curcumin in a few cases of CL in humans (phase 0 of clinical trials).

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethical Committee of the Faculty of Veterinary Medicine, University of Tehran, Iran (Code: IR.UT.VETMED.REC.1402.004).

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interests.

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