Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/n95x4973

CURCUMIN AS A NOVEL TREATMENT FOR HEMOGLOBINOPATHIES: MECHANISMS AND EFFICACY AND CLINICAL APPLICATIONS OF CURCUMIN

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Abstract

Since ancient times, plant-based remedies and their constituents have been highly regarded for health management. Numerous studies involving animal models and clinical trials have demonstrated the beneficial effects of medicinal plants in disease control through the modulation of various biological activities (1, 2). Natural products and their derivatives have gained significant popularity in health management, with their importance documented in religious texts, including the Bible and Quran. Prophet Mohammad (Peace Be Upon Him) also recommended various plants for disease cure and prevention.

In this context, turmeric (*Curcuma longa*) and its key component, curcumin, have been used for thousands of years in the treatment of various diseases due to their efficacy, affordability, and rich source of antioxidants (3). Toxicity studies have shown that curcumin is quite safe, even in high doses (up to 12 grams in humans) (4). Curcumin, the primary constituent of turmeric, has been proven to possess clinical therapeutic properties, with its antioxidant effects playing a vital role in managing chronic inflammatory diseases (5).

Previous research has demonstrated curcumin's therapeutic potential as an antifungal, antiviral, antioxidant, and anti-inflammatory agent, along with its ability to manage other pharmacological activities (6, 7). In this review, we summarize the therapeutic roles of curcumin in disease prevention, including cancer, diabetes, cardiovascular diseases, and other ailments, through the modulation of biological activities (8, 9, 10, 11).

Introduction

Since ancient times, plant-based remedies and their constituents have been highly regarded for health management (1). Numerous studies involving animal models and clinical trials have

demonstrated the beneficial effects of medicinal plants in disease control through the modulation of various biological activities (2). Natural products and their derivatives have gained significant popularity in health management, with their importance documented in religious texts, including the Bible and Quran. Prophet Mohammad (Peace Be Upon Him) also recommended various plants for disease cure and prevention.

In this context, turmeric (*Curcuma longa*) and its key component, curcumin, have been used for thousands of years in the treatment of various diseases due to their efficacy, affordability, and rich source of antioxidants (3). Toxicity studies have shown that curcumin is quite safe, even in high doses (up to 12 grams in humans) (4). Curcumin, the primary constituent of turmeric, has been proven to possess clinical therapeutic properties, with its antioxidant effects playing a vital role in managing chronic inflammatory diseases (5).

Recent research has further highlighted curcumin's therapeutic potential as an antifungal, antiviral, antioxidant, anti-inflammatory agent, and its ability to manage other pharmacological activities (6). Innovations in delivery systems, such as nanoparticles and liposomal formulations, have enhanced its therapeutic efficacy by improving solubility and systemic absorption (7). In this review, we summarize the therapeutic roles of curcumin in disease prevention, including cancer, diabetes, cardiovascular diseases, and other ailments, through the modulation of biological activities (8).

Possible Mechanisms of Curcumin in Health Management

Curcumin plays a crucial role in disease prevention through the modulation of various biological processes. It helps prevent pathogenesis due to its effective scavenging of reactive oxygen species (ROS) (9). Curcumin acts as a potent scavenger of both ROS and reactive nitrogen species, and its antioxidant activity has been demonstrated through the inhibition of controlled initiation of styrene oxidation (10).

The anticancer properties of curcumin are largely attributed to its antioxidant effects, which help control DNA damage and free radical-mediated lipid peroxidation (11). Curcumin is also significant in health management due to its anti-inflammatory effects. While the exact mechanisms of its anti-inflammatory actions are not entirely understood, it is believed that curcumin inhibits enzymes such as cyclooxygenase-2 (COX-2) and 5-lipoxygenase, playing a role in disease management by inhibiting the pathogenesis of diseases (12).

Curcumin in Disease Management: Mechanisms and Effects

Antioxidant Activity

The antioxidant activity of herbs plays a crucial role in health management through the neutralization of free radical species. In vitro studies have shown that curcumin is an effective scavenger of reactive oxygen species (ROS) and reactive nitrogen species (9). Other studies have established its antioxidant activity through the inhibition of controlled initiation of styrene oxidation (10). The potent anticancer properties of curcumin are attributed to its antioxidant effects, which control DNA damage and free radical-mediated lipid peroxidation (11). Curcumin also exerts a powerful inhibitory effect against hydrogen peroxide-induced damage in human keratinocytes and fibroblasts (13). Additionally, curcumin has been shown to improve the activity of detoxifying enzymes such as glutathione-S-transferase (GST) (14). Earlier studies reported that curcumin efficiently inhibits intracellular amyloid toxicity at low dosages in rats through its free radical scavenging activity (15). Experiments based on rat models confirmed that oral administration of curcumin significantly reverses lipid peroxidation, brain lipids, and enhances glutathione levels (16).

Antidiabetic Activity

Studies investigating the effects of curcumin have found that its administration enhances the activities of all antioxidant enzymes (17). Furthermore, curcumin-treated rats showed a significant increase in the expression of genes such as insulin-like growth factor-1, B-cell lymphoma 2,

superoxide dismutase, and GST compared to nondiabetic and diabetic untreated rats (18). Another study on rats demonstrated that curcumin increased insulin secretion, heme oxygenase (HO)-1 gene expression, and HO activity in isolated islets of Langerhans (19). Recent research summarized curcumin's role in the prevention or delay of diabetic retinopathy through the modulation of various biological activities (20). Oral administration of curcumin at a dose of 0.05% w/w in diets for nine weeks showed its role in inhibiting diabetes-induced increases in acetylated histones in the retinas (21).

Anti-inflammatory Activity

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used worldwide to treat inflammation but often cause adverse side effects like gastric ulcers. Curcumin has shown a significant effect in preventing inflammatory processes by modulating or inhibiting various molecular pathways (22). In animal models, curcumin inhibited arachidonic acid metabolism and skin inflammation through the downregulation of cyclooxygenase and lipoxygenase pathways (23). Previous studies have shown that curcumin reduces neutrophil infiltration in inflammatory conditions (24). Other research demonstrated that curcumin inhibited arthritis at a dose of 40 mg/kg, with no acute toxicity observed at doses up to 2 g/kg body weight (25). Curcumin's anti-inflammatory effects in murine colitis models are exerted through the inhibition of COX-2 and pro-inflammatory cytokine expression, as well as the suppression of nuclear factor kappa B (NF-κB) activation (26). Curcumin supplementation has been linked to lowered plasma levels of tumor necrosis factor-alpha (TNF-α), interleukin-6, and monocyte chemoattractant protein-1 in diabetic rats and high glucose-treated monocytes (27).

Antimicrobial Activity

The rise in drug resistance against microorganisms is a significant global concern. Curcumin, a primary component of turmeric, has demonstrated antibacterial, antiviral, and antifungal activities (28). Studies have shown that curcumin exhibits inhibitory activity against methicillin-resistant *Staphylococcus aureus* strains with minimum inhibitory concentration values of 125–250 μg/mL (29). Curcumin has also inhibited the growth of all *Helicobacter pylori* strains in vitro, which were isolated from patients with gastrointestinal disorders (30). It possesses antibacterial properties against various Gram-positive and Gram-negative bacteria.

Effect on Hypertension

Hypertension is a major factor in the pathogenesis of various diseases. Curcumin has proven effective in preventing hypertension. Studies have shown that blood pressure increases due to N-nitro-L-arginine methyl ester can be partially prevented by piperine or curcumin, with the combination being less significant (31)Additionally, curcumin has shown a hypertension-reducing effect (32).

Anti-tumor Activity

Natural products, including those derived from plants, play significant roles in tumor prevention. Curcumin inhibits the activity of drug-metabolizing enzymes (cytochrome p450 and p450 reductase) (33). Animal studies have found that dietary curcumin increases the activity of Phase II enzymes, such as GSTs (34), and down regulates vascular endothelial growth factor through inhibition of peroxisome proliferator-activated receptor δ in colon cancer cells (35). Curcumin reduces cell viability, induces apoptosis, and down regulates Notch-1 and NF-κB (36). It has been shown to induce apoptosis and inhibit the proliferation of melanoma cells (37).

Effect on Respiratory Disorders

Respiratory disorders such as asthma, bronchitis, and colds are increasing due to environmental pollutants. Curcumin shows valuable roles in controlling respiratory complications. Studies have

demonstrated that curcumin increases the expression of cathepsins K and L in the lung, affecting lung fibroblast cell behavior (38). Oral administration of curcumin has inhibited bleomycin-induced pulmonary fibrosis in rats (39) and cigarette smoke-induced lung inflammation and emphysema in mice (40). Curcumin is a potent anti-inflammatory agent that prevents the release of TNF-α and protects against the pulmonary and cardiovascular effects of diesel exhaust particles (41,42).

Immunomodulatory Effect

Curcumin, an active compound in turmeric, plays a crucial role in immune system modulation. Studies have shown that curcumin imparts immunosuppression by down-regulating CD28 and CD80 and up-regulating CTLA-4 (43). Curcumin inhibits lymphocyte proliferation induced by concanavalin A, phytohemagglutinin (PHA), and phorbol-12-myristate-13-acetate (44). It also inhibits PHA-induced T-cell proliferation, interleukin-2 production, nitric oxide generation, and lipopolysaccharide-induced NF-κB, augmenting NK cell cytotoxicity (45). Curcumin modulates the activation of T cells, B cells, macrophages, dendritic cells, cell cycle proteins, and both cell-mediated and humoral immunity 46).

Anti-malarial Activity

Malaria, caused by blood parasites, is a significant health issue in terms of morbidity and mortality. Plants like Carica papaya are important in malaria prevention. Experiments on mice infected with malaria parasites showed that oral curcumin administration reduced blood parasitemia by 80%-90% and significantly enhanced survival (47). Curcumin exhibited cytotoxic effects against Giardia lamblia, inhibiting parasite growth and inducing morphological alterations and apoptosis-like changes (48).

Nephroprotective Effect

Curcumin's effect on renal function and oxidative stress in streptozotocin-induced diabetic rats was examined, showing that treatment with curcumin for two weeks significantly attenuated renal dysfunction and oxidative stress (49). Previous studies have confirmed curcumin's protective effects against nephrotoxicity (50).

Reduction in Sperm Motility

Studies have investigated curcumin's sperm-immobilizing effects, finding that incubation of normal human sperm with curcumin results in a dose- and time-dependent loss of sperm motility (51). Further research on male albino rats showed that crude extracts of Curcuma longa reduced sperm motility and density in treated groups (52,53).

Radiosensitizer Effect

Curcumin has been found to confer radiosensitizing effects in prostate cancer cell lines (54). Studies confirmed that curcumin inhibits the growth of human prostate cancer cells and acts as a promising radiosensitizer in other cancer cells (55).

Clinical Studies on Hemoglobinopathies

Several clinical studies have investigated the effects of curcumin on hemoglobinopathies:

- **Beta-thalassemia**: A double-blind randomized controlled trial showed that curcumin supplementation significantly reduced liver enzyme levels and improved liver function in patients with beta-thalassemia major (56).
- **Sickle cell disease**: Preliminary studies suggest that curcumin may reduce the frequency of pain crises and improve overall quality of life in sickle cell patients (57).

How curcumin acts on sickle cell disease (SCD) and hemoglobinopathies:

Sickle Cell Disease (SCD)

1. **Pain Management**: Curcumin has been shown to reduce pain in SCD patients by targeting the underlying mechanisms of pain. A study demonstrated that topical transdermal curcumin gel significantly decreased hyperalgesia (increased sensitivity to pain) in sickle cell mice models. This suggests that curcumin could be a potential therapeutic agent for managing pain in SCD patients (58).
2. **Anti-inflammatory Effects**: Curcumin's anti-inflammatory properties may help reduce the inflammation associated with SCD. It inhibits the production of inflammatory cytokines and reduces oxidative stress, which can help alleviate symptoms and prevent complications (58).
3. **Antioxidant Properties**: Curcumin acts as an antioxidant, neutralizing free radicals and reducing oxidative stress, which is a significant factor in the pathophysiology of SCD. This can help protect red blood cells from damage and improve overall health (58)..
4. **Vaso-occlusive Crisis Prevention**: Curcumin has been found to be effective in preventing vaso-occlusive crises (59). which are a major complication of SCD. By reducing inflammation and oxidative stress, curcumin can help prevent the blockage of blood vessels that leads to these painful episodes (58)..

Hemoglobinopathies

1. **Beta-thalassemia Major**: A clinical trial investigated the effects of oral curcumin on liver function in patients with beta-thalassemia major. The study found that curcumin significantly decreased levels of liver enzymes (AST, ALT, ALP, and bilirubin) in the treatment group compared to the placebo group (60). This suggests that curcumin has beneficial effects on liver function in patients with beta-thalassemia major.
2. **General Hemoglobinopathies**: Curcumin has been shown to ameliorate the negative effects of hemoglobin disorders and the side effects of therapies. Its anti-inflammatory, antioxidant, and analgesic properties make it a potential therapeutic agent for managing symptoms and improving quality of life in patients with hemoglobinopathies (61).

Effect of Curcumin on Endometriosis

Endometriosis is a chronic gynaecological disorder representing the implantation of endometrial glands and stroma outside the uterine cavity (62) It affects adolescents and reproductive-aged women and is commonly associated with infertility, dyspareunia, dysmenorrhea and chronic pelvic pain (64). The pathogenesis of endometriosis has not been fully understood. To date, nearly all current treatment options for endometriosis suppress endometrial function and are not curative. Combined oral contraceptives and progestins are commonly prescribed as first-line therapy to alleviate pain symptoms. However, if the first-line therapies are ineffective, contraindicated or not tolerated, gonadotropin-releasing hormone-agonists are prescribed. In case of resistance to other treatments, an aromatase inhibitor is prescribed (63-65). Presently, curcumin was found to have anti-endometriosis, antioxidant and anti-inflammatory properties

Discussion

The findings from these studies indicate that curcumin holds significant therapeutic potential for patients with hemoglobinopathies. For instance, **curcumin supplementation has been shown to significantly reduce liver enzyme levels and improve liver function in patients with beta-thalassemia major** (70). Additionally, preliminary studies suggest that **curcumin may reduce the frequency of pain crises and improve overall quality of life in patients with sickle cell disease** (71-73).

These promising results highlight the multifaceted benefits of curcumin, ranging from its antioxidant and anti-inflammatory properties to its potential in managing chronic diseases. However, despite these encouraging findings, there is a clear need for more extensive and rigorous clinical trials to validate the efficacy of curcumin in treating hemoglobinopathies. Larger sample

sizes and longer study durations are essential to confirm these effects and to establish optimal dosing regimens that ensure safety and maximize therapeutic outcomes.

Moreover, the variability in curcumin's bioavailability remains a challenge. Advances in delivery systems, such as nanoparticles and liposomal formulations, have shown promise in enhancing curcumin's solubility and systemic absorption (74-75). Future research should focus on optimizing these delivery mechanisms to improve the bioavailability of curcumin, thereby enhancing its clinical efficacy.

In conclusion, while the current body of research supports the potential benefits of curcumin in managing hemoglobinopathies, further large-scale studies are necessary to substantiate these findings. Such research will be crucial in integrating curcumin into standard therapeutic protocols for hemoglobinopathies, ultimately improving patient outcomes and quality of life.

Conclusion

Curcumin shows promise as a complementary therapy for hemoglobinopathies due to its anti-inflammatory, antioxidant, and iron-chelating properties (60,64,65&66) Future research should focus on conducting rigorous clinical trials to validate these findings and explore the full potential of curcumin in managing hemoglobinopathies (67&68).

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