

AN EXPLORATION OF THERAPEUTIC ASPECTS AND DRUG DELIVERY SYSTEMS OF CURCUMIN

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Abstract

Curcumin, a phenolic compound can be extracted from the rhizome part of *Curcuma longa* linn as well as it is most seen in tropical southeast part of Asia. It was known that it belongs to the family Zingiberaceae. The name of the plant is specific to different countries. In addition to its medicinal use, this plant has been used in cooking for its spice and color. Its medicinal use has been proven in various ayurvedic medicine. This review focuses on exploring various therapeutic activities exhibited by curcumin and its distinct drug delivery systems that contribute for the enhancement of those therapeutic actions. Therapeutic aspects include anti-inflammatory, antioxidant, antimicrobial, antidiabetic, anticancer, wound healing, antiaging, neuroprotective activities of curcumin have been explored. Anti-inflammatory and antioxidant pave the way for the management of variable pathologic conditions. Some of the clinical trials which expose the various therapeutic activity of curcumin have been discussed. Drug delivery systems has been emerged for achieving the desired curative effects of drug in concern with safety. This drug delivery system approaches to development of different formulations and several therapeutic transporting systems of drug. Different types of drug delivery systems like nano formulations, polymeric micelles, hydrogels, and phospholipid complexes of curcumin which helps in supporting therapeutic activity and in overcoming the barriers of curcumin have been discussed.

KEYWORDS: Curcumin, therapeutic effects, drug delivery systems, anti-inflammatory, antioxidant.

INTRODUCTION:

Curcumin, a phenolic compound can be extracted from the rhizome part of *Curcuma longa* linn as well as it is most seen in tropical southeast part of Asia. It was known that it fits to the family Zingiberaceae. The plant name is specific to different countries. In addition to its medicinal use, this plant has been used in cooking for its spice and color. Its medicinal use has been proven in various ayurvedic medicine. The compound can be isolated in the form of chromatographic separations. ¹ Presently accessible curcumin preparations comprise roughly 77% diferuloylmethane (curcumin); 18% of these preparations comprise demethoxycurcumin; and 5% of them comprise bisdemethoxycurcumin. '3–5%' curcuminoid constitutes turmeric. Curcumin, nevertheless, gives rise to the principal biological activity of turmeric. Most of the plants are made up

of curcumin and two other similar chemicals, bisdemethoxycurcumin and dimethoxycurcumin. Diarylheptanoid compounds are what these are. Moreover, curcuminoids are all three of these chemicals.

Various clinical studies on curcumin have been conducted to figure out the biological properties of curcumin. ² Curcumin is known for its potent biological properties. Curcumin is an aromatic compound, and it has chemical formula and molecular weight as $C_{21}H_{20}O_6$ and 368.38 respectively. ³ Recently curcumin has been distinguished as PAINS and IMPS compound. PAINS, imply for pan assay interference compounds, are the substances which can contribute to activity in various types of assays opposed to development of target and compound interactions. Curcumin has been shown to contribute distinct behaviors of PAINS compound. Evidence shows that

IMPS is said to be invalid metabolic panaceas can be seen in center part of the natural products in black hole which depletes resources of research. Regarding pharmacokinetic parameters, evidence reveals that curcumin dose of 12g/day is well tolerated for absorption without any negative impacts. Distribution of curcumin has been studied in variable assays and animal models. It has been reported that this compound has variable distribution and not to any specific organs. Studies revealed that curcumin is metabolized by both the phases of metabolism. After metabolism, the conjugates of curcumin have been excreted in urine whereas the unabsorbed part is degraded.⁴ This review focuses on exploring various therapeutic activities of curcumin and its distinct drug delivery systems that contribute for the enhancement of those therapeutic action.

THERAPEUTIC ACTIVITY OF CURCUMIN:

ANTI-INFLAMMATORY:

Inflammatory pathway can be initiated in distinct ways in regards with various triggers of inflammation. Identifying the root cause of inflammation is essential for choosing the anti-inflammatory drugs. Anti-inflammatory drugs exhibit various mechanism for prevention and management of inflammatory disorders. Inflammatory mediators are responsible for induction of inflammatory pathways. The positive impact of curcumin towards inflammation is through acting on signaling pathway and on inflammatory mediators. Curcumin acts on various inflammatory receptors including Toll-like receptors, nuclear factor kappa-B, mitogen-activated protein kinases, activated protein kinases, activator protein-1. By acting on these pathways, it inhibits both pro-inflammatory and inflammatory mediators.⁵ The curative effect of curcumin for inflammation helps in the management of various inflammatory disorders. It serves as a therapeutic option for chronic inflammation.⁶

ANTIOXIDANT:

Antioxidant property in curcumin helps in the management of various diseases. Free radicals and radical species are responsible for oxidative reactions. Increase in oxidative stress is the major etiology of various pathologic conditions. Antioxidants from natural sources can be used for various disease conditions. Many studies have been conducted for evaluating antioxidant activity of curcumin. The derivatives of curcumin like demethoxycurcumin and bisdemethoxycurcumin were also found to possess antioxidant activity.⁷ Curcumin has capacity of scavenging the free radicals and reactive oxygen species (ROS) in consideration of decreasing the oxidative stress. Additionally, it exhibits antioxidant activity by activating the antioxidant enzymes that have the capability to neutralize free radicals. Curcumin acts on nuclear factor erythroid 2-related factor 2 (Nrf2) pathway to detoxify the enzymes and decrease the oxidative stress. Curcumin also acts as chelating agent on metal ions which are responsible for free radical generation.⁸

ANTI-DIABETIC:

Diabetes mellitus can be expressed by elevated blood glucose levels. Various distinct classes of antidiabetic drugs have been developed for the management of diabetes mellitus. Adverse events of these antidiabetic drugs pave the way for development antidiabetic herbal products. Chronic inflammation due to release of proinflammatory mediators in adipose tissues can constitute insulin resistance of diabetes mellitus. It can be complicated due to the action of angiotensin like protein 2 (ANGPTL2) with its role in activation of macrophages results in diabetic related complication. Anti-inflammatory effect of

curcumin can exhibit antidiabetic activity.⁹ Hyperglycemia can be presented with the elevation of oxidative stress through reducing the various antioxidant pathways. These pathways lead to the origination of reactive oxygen species leading to the contribution of distinct microvascular complications of diabetes mellitus. Inflammation along with oxidative stress serves as one among the etiology of diabetes mellitus. Curcumin with its anti-inflammatory along with antioxidant activity helps for the management of diabetes mellitus.¹⁰

ANTI MICROBIAL:

Curcumin has been investigated for its antimicrobial activity towards most of the microbes (bacteria, fungi, and pathogens). Out of distinct types of bacteria, curcumin exhibits more promising activity towards helicobacter pylori. This activity helps in the treatment of gastritis. The antiviral effect of this compound helps in the development of its derivatives. Significant antifungal activity of curcumin has been seen against Candida species and Paracoccidioides brasiliensis.¹¹ Curcumin with its analogues exhibits antiviral activity by inhibiting the multiplication of diverse groups of viruses.¹² Adding to that, curcumin has negative impact on microbes with capacity of causing surgical infections, infection caused by medical devices, and with microbes resistant to antibiotics. The antimicrobial activity of curcumin is by acting on cytoskeleton of bacteria responsible for the cell division and on protein which is responsible for microbial cell division. Studies revealed that the antibacterial activity exhibited by curcumin is because of its methoxy and hydroxy derivatives.¹³

ANTI-CANCER ACTIVITY

Chronic inflammation combined with oxidative stress serves as a major part in the pathophysiology of cancer. Curcumin has the capability to inhibit various inflammatory pathways as well as neutralize free radicals. These combined effects of anti-inflammatory along with antioxidant of curcumin contribute to inhibiting the progression of cancer. Cancer cells have the capacity to inhibit the apoptosis process. Apoptosis is the process of eliminating abnormal cells from the body. Curcumin has the ability to activate the apoptosis process thereby resisting the growth and proliferation of cancer cells. Cell cycle regulates the division of human cells. Cancer cells has the ability to act on this cycle resulting in multiplication cancer cells. Curcumin helps for the regulation of cell cycle along with arresting the growth of cancer cells. It acts on distinct signaling pathways like pathway of JAK/STAT to constrain the progress for cancer cells. These pathways are responsible for anticancer activity.¹⁴

WOUND HEALING ACTIVITY

As we discussed earlier, curcumin exhibits various therapeutic activity required for the healing of wounds. It reduces inflammation and prevents the cells from being exposed to oxidative distress. Since wounds are more prone to infection, anti-infective property acts for the prevention of infection. Curcumin helps in collagen synthesis from fibroblast cells leading to the deposition of collagen resulting in speeding up the process of wound repair. Matrix metalloprotein activity has been regulated by curcumin in order to prevent the degradation of tissues. Adding to that, analgesic properties support the healing process of curcumin.¹⁵

ANTI-AGING ACTIVITY:

Curcumin has gained attention for anti-aging activities. Aging can be modulated by various factors including genetics, and

lifestyle. Curcumin activates cellular homeostasis in the form of enhancement of autophagy. Environmental factors cause. Impaired DNA function occurs when exposed to various environmental factors. Curcumin has the ability to exert DNA protective effects. Shorten telomerase contributes to aging of cells. Curcumin can lengthen telomerase activity and helps in delaying the aging process. It enhances the skin health. ¹⁶

CARDIOPROTECTIVE ACTIVITY:

Curcumin exerts cardioprotective action in the form of various distinct therapeutic activities. Endothelial dysfunction, contraction of blood vessels, rise in blood pressure, thrombosis serves as a major risk factor of cardiovascular disorders. Curcumin showed positive effects in increasing nitric oxide production and helps in vasodilation. The formation of thrombosis and platelet aggregation can be inhibited in the form of antiplatelet activity. Cholesterol levels have also been decreased by the action of curcumin. Accumulation of myocardial fibers and signaling pathway of cardiac hypertrophy

can be inhibited by the action of curcumin. It also regulates the electrophysiology of the heart. It plays a pivotal role in decreasing myocardial ischemia-reperfusion injury. ¹⁷

NEUROPROTECTIVE ACTIVITY:

Curcumin exhibits neuroprotective effects in the form of various pathways. Inflammation is the initial stage for most neurological disorders. The anti-inflammatory property of curcumin helps in preventing the harmful effects of neurons. Reducing oxidative stress also helps in decreasing the progression of neurodegenerative diseases. Curcumin has the potential to activate neurogenesis thereby helping in maintaining proper cognitive function. Additionally, it helps in the proper regulation of neurotransmitters like serotonin and dopamine, this in turn helps in maintaining proper brain function. Curcumin helps in inhibiting the formation and accumulation of amyloid-beta plaques. These plaques are responsible for some neurodegenerative disorders like Alzheimer’s disease. ¹⁸

Table 1. Clinical trials expose various therapeutic aspects of curcumin.

SI. NO.	Study			Comparative Drug / placebo	Activity	Disease	Parameters	Outcome
	Design	Duration	Sample size					
	Randomized, open-label, parallel, active controlled	28 days	139	Diclofenac	Anti inflammatory	Knee osteo arthritis	Knee Injury and Osteoarthritis Outcome Score (KOOS)	For patients diagnosed with knee OA, curcumin three times a day offers a better safety profile and comparable efficacy to diclofenac two times a day.
	Double-blind randomized controlled clinical trial	12 weeks	61	Placebo	Antioxidant	β- Thalassemia	Serum malondialdehyde (MDA), total and direct bilirubin	When combined with deferoxamin, curcumin supplementation enhanced the antioxidant state in significant β-thalassemia patients.
	Double blind Randomized placebo control add-on clinical trial	3 months	70	Placebo	Anti diabetic	Type II Diabetes mellitus	Fasting blood glucose (FBG), Glycated hemoglobin (HbA1c)	Outcome of this study reveals that the nanocurcumin provided beneficial impact in type 2 diabetes mellitus patients by reducing the HbA1c levels along with BMI and LDL-C.
	Double-blind, placebo-controlled randomized trial	6 months	97	Placebo	Anti-cancer	Prostate Cancer who received intermittent androgen deprivation (IAD)	Prostate specific antigen (PSA)	Oral curcumin use for six months had no discernible effect on the length of time IAD patients spent off medication overall. On the other hand, throughout the curcumin administration phase, curcumin intake decreased PSA rise. This dosage of curcumin was safe and well acceptable.
	Randomized, double-blind, placebo-controlled trial	12 weeks	60	Placebo	Wound healing	Diabetic foot ulcer	Total- and LDL-cholesterol, TAC, and	Consuming nanocurcumin significantly revealed controlled glycemic levels, total and LDL cholesterol, TAC, and

							Glutathione	GSH significantly in DFU patients, but it had no effect on ulcer size markers.
	Double-blinded, randomised, placebo-controlled,	4 weeks	70	Placebo	Cardio protective	Hypercholesterolemia individuals	Total and LDL-cholesterol	More cholesterol is lowered when curcumin is added to phytosterol therapy than when phytosterol therapy is used alone.
	Pilot, randomized, triple-blind, placebo-controlled, add-on trial.	9 months	30	Placebo	Neuro protective	Parkinson's disease	Movement disorder society- Unified Parkinson disease rating scale (MDS-UPDRS part III)	Despite being a naturally occurring substance that is well tolerated, curcumin did not improve the quality of life or reduce the clinical symptoms of Parkinson's disease patients in this trial.

Table 1. expose the various therapeutic activity of curcumin. The study design, sample size and duration have been mentioned. Parameters responsible for exhibiting the therapeutic activity of curcumin have been mentioned. Adding to that, outcome of the clinical trials expressing the therapeutic activity of curcumin was mentioned.

DRUG DELIVERY SYSTEMS OF CURCUMIN:

In order to achieve the desired therapeutic outcome from a drug molecule, it should be available in the specific pathologic area for a long time. The accumulation of drug in the body for a long time can result relative harmful effects. Drug delivery systems has been emerged to achieve the desired beneficial effects of drug in concern with safety. This drug delivery system approaches to development of different formulations and several therapeutic transporting systems of drug.¹⁹ The poor solubility, decreased bioavailability, faster metabolism of curcumin constitutes the essentiality of development of drug delivery system.

NANOFORMULATIONS:

The poor solubility, decreased bioavailability, faster metabolism of curcumin constitutes the essentiality of development of drug delivery system. In order to overcome these challenges nano formulation curcumin has emerged. The nano formulation of curcumin is in the form of nanoparticles, nano capsules, and liposomes for treating diverse pathologic conditions. The pharmacokinetics of curcumin can be improved by the action of encapsulating curcumin.²⁰ The nano formulation of curcumin has its therapeutic potential in the treatment of high-risk diseases like cancer, cardiovascular diseases, stroke, inflammatory diseases. The nanoparticles of curcumin showed positive effect in increasing the bioavailability of curcumin because of its smaller size. The microenvironment of cells helps in release of curcumin by degrading the nanoparticles. Smaller size helps in increasing the soluble nature of curcumin as well as helps in increasing the bioavailability to reach the targeted sites. Nanoparticles of curcumin help in protecting it from heat and pH of the body.²¹

POLYMERIC MICELLES:

Curcumin can be encapsulated with polymeric micelles has self-colloidal systems made with molecules that easily soluble in aqueous solutions. Polymeric based drug delivery system uses biodegradable substances like poly (lactic-co-glycolic acid) to control the kinetics of curcumin. Polymeric micelles have been improved to overcome the disadvantages of pharmacokinetic properties of curcumin. The advantage of polymeric micelles is that they can be made easily for biocompatible with its physical and chemical properties. Polymeric micelles help the curcumin to increase its soluble nature as well as to prolong the circulation in blood. Additionally, it helps in achieving the targeted passive drug delivery by increasing the penetration of curcumin.²²

HYDROGELS:

Hydrogels are three-dimensional polymers with hydrophilic nature that increase the absorbing capacity of the molecule in water or in biological fluids. Induction of curcumin with hydrogel polymers helps in the development of wide benefits for the therapeutic action curcumin. Hydrogels enhance the sustainability of curcumin for a prolonged period with its hydrogel matrix. It can also enhance the stability of curcumin. Majorly, it provides the benefits for the directed delivery of curcumin towards the therapeutic sites for inflammation or injury by acting on particular receptors or ligands. Combining hydrogels of curcumin with other therapeutic herbs produces similar impact for the improvement of therapeutic aspects of curcumin. The modification of characteristics and kinetic properties of hydrogels has the capacity to improve optimum release at the specific site. This formulation helps curcumin for wound healing and inflammation.²³

PHOSPHOLIPID COMPLEXES OF CURCUMIN:

Curcumin can be formulated with phospholipid complexes to enhance its drug delivery. The phospholipid complexes are molecules composed of head with water soluble in nature and base with hydrophobic in nature. This molecule makes complexes with compounds of curcumin which are poorly soluble in nature. This complex helps in increasing the absorption of drug in the body. Since the absorption has been increased the dose of the curcumin required to exert therapeutic effects will be reduced. This in turn contributes to decreasing the

risk of dose related adverse effects. Variable procedures are available for making this complex namely evaporation and precipitation. Phospholipids and curcumin should be mixed in proper quantities and the solvent should be precipitated for the formation of phospholipid complexes.²⁴

CONCLUSION:

Curcumin exerts a pivotal role in the cure of various pathologic conditions. Various clinical trials revealed evidence for the exploration of beneficial action against variable pathologic conditions. In contrast to these beneficial therapeutic actions, curcumin has disadvantaged in pharmacokinetic properties. To overcome this barrier, various modulation in drug delivery systems for curcumin has been addressed. Clinical trials of curcumin provided evidence for exploring the therapeutic aspects of curcumin. This article acts as a driving force in exploring both therapeutic aspects and drug delivery systems of curcumin.

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