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BIOMEDICAL ACTIVITY OF CURCUMIN AND SCIENTIFIC WAYS TO ENHANCE ITS PHARMACO-KINETIC NATURE

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Abstract

Turmeric rhizomes (*Curcuma longa* L.) from a family of Zingiberaceae are widely grown in Southeast Asia, India, and Indonesia. Curcuminoids belong to diferuloylmethane group and coexist in *keto* and *enol* form while *enol* form is more stable energetically. Curcumin is well-known for its health-promoting impacts such as antidiabetic, antimicrobial, antioxidant, anti-inflammatory and anticancer activities. This review seeks to provide an in-depth discussion of curcumin' usage within its effect on health support and disease prevention. Curcumin's bioavailability, bio-efficacy and bio-safety characteristics are discussed. Finally, amidst curcumin's multifaceted uses, its instability and low bioavailability, pharmacokinetic ability, nanoparticle range are viewed.

Keywords: Curcumin, biomedical benefits, enhancing pharmacokinetics.

1. Introduction

Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione), also known as diferuloylmethane, stands as the primary constituent of turmeric, derived from the rhizome of Curcuma longa (Figure 1), a plant native to Southeast Asia and part of the Zingiberaceae family (ginger family) [1]. The genus Curcuma contains about 120 species. Apart from volatile oils and oleoresins, C. longa contains three different curcuminoids (Figure 2): 75–80% curcumin, 15–20% demethoxycurcumin, and 3–5% bisdemethoxycurcumin. These are also present in other curcuma species, albeit in lower concentrations.

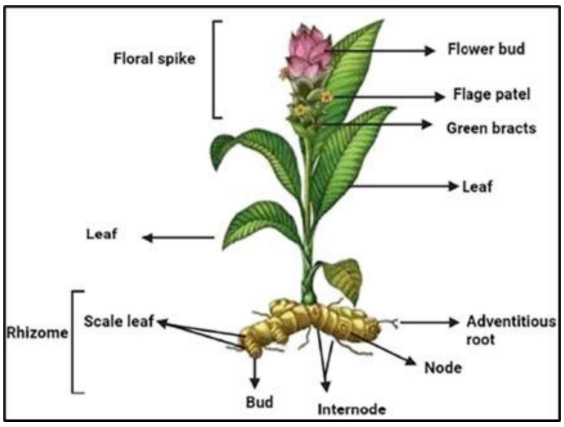

Fig 1. The curcumin plant [2-3]

Curcumin, constituting approximately 2–5% of turmeric, not only provides the spice its characteristic yellow hue but also accounts for a significant portion of its therapeutic properties.

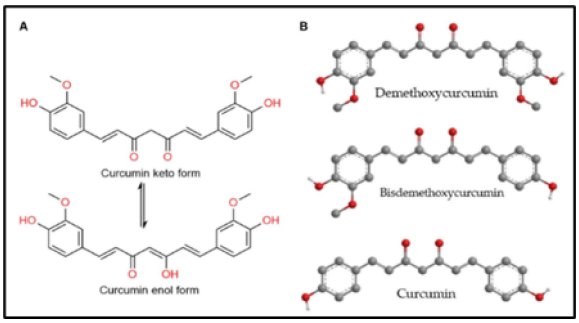

Fig. 2. (A) The tautomerization of the curcumin molecule. (B) Curcuminoids – the main yellow pigments found in turmeric [4]

In addition to its use as a flavoring and coloring ingredient

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in food, turmeric holds on a prominent place in Ayurvedic medicine due to its analgesic, antioxidant, antiseptic, antimalarial, and anti-inflammatory, antibacterial, antiviral, antidiabetic and wound-healing effects attributes (Figure 3) [5-6]. For thousands of years, curcumin has been used in traditional Chinese medicine and Ayurveda to combat inflammation and bacterial infections. making it an appealing subject of current pharmacological research [7-8].

These properties are primarily attributed to curcumin's ability to modulate multiple molecular targets and signalling pathways implicated in the pathogenesis of cancer. This includes modulation of NF-κB and STAT3, frequently overexpressed in head and neck tumor cells, the regulation of p53 protein in breast cancer cell lines as well as interference with cellular pathways in prostate cancer. In vitro and in vivo studies demonstrate curcumin's ability to inhibit proliferation, decrease viability, and induce apoptosis in cancer cells. Curcumin in combination with epigallocatechin gallate has been effective in reducing tumor volume in animal models [9-10].

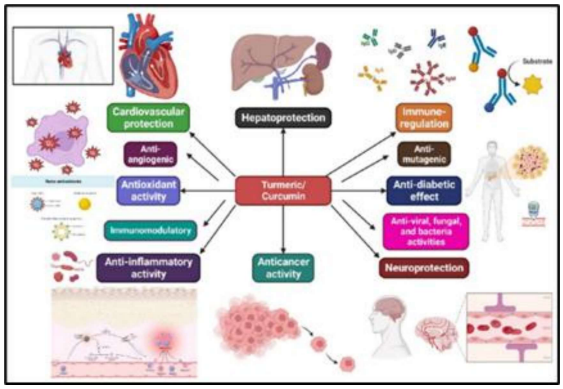

Fig. 3. Effects of curcumin on human health

However, the pharmacokinetic properties of curcumin limit its clinical application. Poor solubility, low intestinal absorption rates, and rapid metabolism and elimination from the body result in low bioavailability. Approaches for improvement include the combination of curcumin with additives like piperine, an active component of black pepper, which increases bioavailability by 2000%. Another possibility to improve bioavailability is developing curcumin into phospholipid complexes, liposomes, and nanoparticles [11].

II. Materials and Methods

The objective of this systematic review (SR) is to provide an overview of the current state of research on the biomedical use of curcumin and its pharmacokinetic evaluation from various spheres. During the preparation of the presented review, scientific articles that were published after 2020 from Pubmed, Scifinder, ScienceDirect, Medline, Embase, Google Scholar, and Web of Science were analyzed. The key terms employed for the search encompassed topics such as turmeric, Curcuma longa, curcuminoids, curcumin, bioavailability, bioactive compounds, pharmacokinetic, pharmacological effects. Additionally, a thorough examination of articles published in peer-reviewed journals was performed through a library search.

III. Chemistry of Curcumin and its Therapeutic Effects

Curcumin, a natural polyphenolic compound, is of great medicinal value. Curcumin possesses numerous biological activities, including anti-cancer, antioxidant, antimicrobial, and anti-inflammatory properties. Curcumin (CUR) is a low molecular weight polyphenol compound obtained from the roots of the Curcuma longa plant and has been used for centuries in Asian medicine. CUR is a promising candidate for the treatment of a number of disorders due to its significant pharmacological benefits, which include anti-inflammatory, anti-cancer, anti-Alzheimer, antimutagenic, antioxidant, and antibacterial properties (Figure 3) [12]. For example, Key structural features contributing to its activity include the o-methoxyphenol group and methylenic hydrogen, which play pivotal roles in its antioxidant properties. These groups enable curcumin to donate electrons or hydrogen atoms to neutralize reactive oxygen species, thereby mitigating oxidative stress.

It also gets readily metabolized and degrades when exposed to heat, light, oxygen or alkaline solutions, thus restricting its potency as a functional molecule. Oral administration is the traditional method for intake of curcumin. However, due to the hydrophobicity of curcumin, it is poorly absorbed by the body. The presence of long hydrocarbon chain and aromatic groups in curcumin makes it a hydrophobic moiety, thus preventing its solubility in aqueous media of the bloodstream [13]. Low bioavailability of any pharmaceutical agent within the body is due to; (1) poor gastrointestinal absorption, (2) high rates of metabolism, (3) inactivity of metabolic products, and (4) rapid elimination and clearance. Because of its tautomeric structure, high-molecular-weight, and aromatic groups, curcumin is extremely hydrophobic and, therefore, only partially absorbed through the gastrointestinal epithelium. The brief half-life of curcumin plays a crucial role in its low bioavailability. Several delivery techniques have been developed to overcome the pharmaco-kinetics predisposing to poor bioavailability of orally ingested curcumin, including adjuvants, nanoparticles, liposomes, and a self-nanoemulsifying drug delivery system (SNEDDS) [14].

IV. pharmacokinetics of curcumin

Pharmacokinetics of curcumin refers to the study of how curcumin is absorbed, distributed, metabolized, and excreted in the body. Here's a brief overview: (1) Absorption: Curcumin has poor bioavailability due to its low solubility and rapid metabolism; (2) Distribution: Curcumin is distributed to various tissues, including the liver, kidneys, and brain; (3) Metabolism: Curcumin is metabolized in the liver and intestine, primarily through glucuronidation and sulfation; (4) Excretion: Curcumin is excreted through the bile, urine, and feces. The bioavailability and pharmacokinetic-related studies of curcumin have shown results indicating its very low absorption in the intestines and speedy removal within the body [15].

Curcumin shows limited bioavailability since it is poorly absorbed, rapidly metabolized, and thus easily eliminated by the body. The absorption of curcumin by the human body is low due to its poor solubility in water (about 11 μg/mL). These features restrict the use of curcumin as a therapeutic agent. Thus, in order to increase the efficacy of curcumin, various methods have been adopted over the years such as liposomal curcumin, curcumin nanoparticles, use of piperine as an adjuvant, etc [16].

Regardless, curcumin's substantial limitations, formulations have come about to improve bioavailability, permeability, circulation, half-life, and withstand metabolic processes. These formulations admit chemical curcumin derivatives and analogs with metabolic adjuvants, nanoparticles, liposomes, micelles, nanostructured lipid carriers (NLC), and phospholipid complexes [17].

4.1. Scientific Ways to Enhance Pharmacokinetics of Curcumin

Curcumin formulations such as nanoparticles, liposomes, micelles, and phospholipid complexes have been developed to enhance bioavailability, circulation, permeability, and resistance to metabolism [18]. Recent advances include novel delivery systems, such as nanoparticles, liposomes, and phospholipid complexes, that enhance absorption and stability [19].

4.1.1. Curcumin glucuronide and Its Pharmacokinetic nature

According to previous research, curcumin and its reductive metabolites can be easily conjugated in vitro and in vivo. When glucuronic acid or sulfate molecules are connected to one of the hydroxyl groups by glucuronidases and sulfotransferases, glucuronide and sulfate O-conjugated metabolites are produced. Despite the finding of isolated liver microsomes with double glucuronidation

and isolated reaction systems with diglutathionylated curcumin, the conjugation process normally involves only a single moiety addition. Although these metabolites have a higher molecular weight than their substrates and are therefore less active than those substances, curcumin glucuronide is a frequent metabolite of curcumin that is detected in body fluids and cells. Curcumin levels in both the blood and urine plasma following oral treatment have been reported to be low in both animal and human experiments. Research results indicated that curcumin is firstly bio-transformed into tetrahydrocurcumin and dihydrocurcumin and at last to conjugates of monoglucuronide. Preliminarily studies on animals described the fast metabolization of curcumin and its conjugation in liver, and, subsequently, with reduced systemic bioavailability, it is excreted in the feces. In different kinds of studies related curcumin's metabolism on rodents, excretion and biodistribution have been reported. The transformation actions of curcumin are shown in Figure 4.

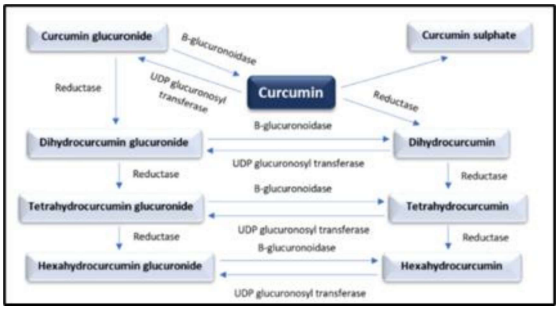

Fig. 4. Metabolite derivatives of curcumin

The change of the liver and intestines may be responsible for curcumin sulfates and curcumin glucuronides generation, or in contrast, it can also reduce molecules like hexahydrocurcumin. Besides glucuronidation, a well-established metabolic pathway for curcumin, it is also essential to consider other metabolic processes like sulfation. Sulfation, mediated by sulfotransferase (SULT) enzymes such as SULT1A3, 1B1, 1C4, and 1E1, results in the production of phase II metabolites, including glucuronides and sulfates. These metabolites account for the majority of circulating curcuminoids in both humans and animals [20].

4.1.2. Pharmacokinetic Enhancement through Piperine

Curcumin's bioavailability is inadequate by poor absorption, rapid metabolism, and quick elimination. [21] Several organic compounds have also been utilized to boost curcumin bioavailability, the majority of which reduce the metabolism of curcumin and enhance its absorption. [22]. To improve its bio-efficacy, strategies like using piperine to inhibit metabolic degradation have been developed. [23]. Piperine is the most widely used chemical because it is the active element in black pepper. Curcumin bioavailability is increased when curcumin is consumed in the form of fresh or powdered turmeric rather than supplements, possibly owing to synergistic involvement with other turmeric components or the impact of the turmeric matrix.

A basic procedure that has been used for boosting up the curcumin's bioavailability is the application of compounds that prevent curcumin's metabolic route activity. Study results on methods of increasing curcumin's bioavailability reported that administration of piperine with oral curcumin, which is actually an alkaloid present in long pepper (Piper longa) and black pepper (Piper nigrum), found out to have an effect on improving the curcumin's serum concentrations in rodents. Additionally, piperine is a powerful inhibitor of glucuronidation of hepatic and intestines. Using increased doses of oral curcumin (2000 mg/kg) along with the piperine, the systemic bioavailability was found to be increased by 154%. Various trials of phase I focused on cancer patients depicted information about pharmacokinetics, human bioavailability of curcumin, and metabolites [20].

4.1.3. Pharmacokinetic Nature and Encapsulated Curcumin

Curcumin's bioavailability can be affected by many aspects, such as grinding, drying, and heating processes, and also by the intake of macronutrients, such as dietary lipids, which can interfere with curcumin's solubility and

absorption. However, the development of curcumin and other compound combinations in different formulations enhanced its bioavailability. These formulations include curcumin nanoemulsion, liposomal curcumin, and even curcumin encapsulation into milk exosomes, which showed higher permeability and bioavailability [23].

A mouse model organism was utilized to evaluate skin inflammation with or without ultraviolet-B radiation exposure and with or without curcumin encapsulation in coconut oil. After 24 h of incubation, the experimental setup treated with encapsulated curcumin had less skin reddening than the control group. Moreover, inflammatory cytokine analyses and histology of the encapsulated curcumin-exposed skin revealed less skin cell damage and reduced inflammation (markers) compared to the control and non-encapsulated groups [24]. The transformation actions of curcumin are shown in Figure 5.

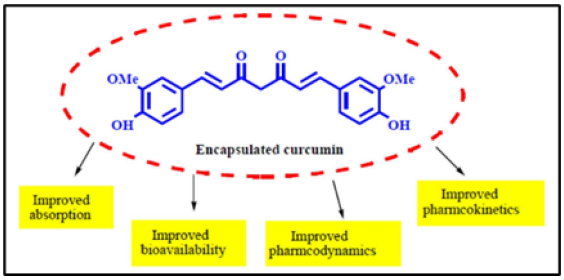

Fig. 5. Benefits of encapsulated curcumin.

Furthermore, in chronic kidney disease subjects, supplementation with 500 mg of curcumin tablets, two times/day for six months, reduced plasma pro-inflammatory mediators and lipid peroxidation. During the long-term administration treatment, no serious adverse events were observed, confirming the safety profile of this compound. In addition, in patients with non-alcoholic fatty liver disease, phytosomal curcumin supplementation of 1000 mg/day in two doses for eight weeks was considered safe and well tolerated with no report of severe adverse events during the treatment [23].

4.1.4. Pharmacokinetic Nature and Curcumin Nano-formulation

Nanomaterials and nanostructures have found considerable interest in various therapeutic applications. The most common nanoformulations of curcumin are solid lipid nanoparticles, nano-composite, nano-suspension, nanoparticles, liposomes, micelles, polymeric nanoparticles, and hydrogels [24]. Because of the decreased curcumin's bioavailability, Theracurmin, which is an artificially extracted nanoparticle type of curcumin, was found having a sophisticated biological availability. Research looking at the pharmacological attributes of Theracurmin in patients without any disease attained acceptable concentrations of plasma after just one dose. Further studies exploring the well-being of curcumin conducted on those with cancer depicted the same results. A nanocarrier composed of super magnetic iron oxide nanoparticles with a coating formed by the combination of three block copolymer Pluronic F127 and F68 on oleic acid was used as a delivery agent for curcumin to kill bone tumors. Magnetic silk fibroin nanoparticles have also been used as delivery system for curcumin. Curcumin delivered by this method exhibited increased cytotoxic effects in human breast adenocarcinoma cell line (MDA-MB-231 cells) [16].

Maximum plasma curcumin concentrations (Median) following 200 mg Theracurmin prescription were found out to be 324 ng/mL, and for dose of 400 mg, Theracurmin maximum plasma level attained was 440 ng/mL, with no expected harmful activities observed during 9 months of research [20]. A nanoparticle formulation of curcumin resulted in 27-fold higher blood levels in humans as compared to the curcumin powder, thus indicating its use as an effective medicinal agent [16]. According to another study, with curcumin nanoparticles, prolonged topical administration and improved bioavailability of curcumin were obtained, including the possibility of skin discoloration. Therefore, nanotechnology is a very effective tool to increase the limits of native curcumin to improve its therapeutic potential due to the presence of other key features such as high cellular uptake,

biodistribution, dissociation rates, stability in serum, and sustained drug release at the target site [24].

4.1.5. Pharmacokinetic Nature and Curcumin-phospholipid complex

Several studies have implied the crucial roles of phospholipids in improving the therapeutic efficiency of small molecules for those with poor oral bioavailability. Theoretically, phospholipid complexes are appropriate strategies for any small bioactive molecule. The curcumin molecule is found to have a high affinity toward biological membranes and tends to penetrate them rapidly to form dimeric biological complexes. Despite being a phenolic and poorly soluble compound, curcumin can link with phospholipids (particularly phosphatidylcholine) by forming non-covalent adducts. At last, the formation of these curcumin–phospholipid complexes could enhance the curcumin pharmacokinetics by stabilizing intestinal pH values and shielding curcumin in terms of retro-Claisen hydrolysis. It is reported that a curcumin–phospholipid complex enhanced the oral bioavailability of curcumin compared with curcumin suspension to fivefold. In addition, pharmacokinetic study results revealed that a phospholipid–curcumin complex implied significantly high plasma concentrations and was found to be more stable when compared to natural curcumin. Various research findings suggest that the phospholipid–curcumin complex is one of the most precious methods for making curcumin more stable and improving its bioavailability [24].

V. CONCLUSION

This review explores the various properties of curcumin, emphasizing its contribution to medicinal benefits and therapeutic properties. Novel aspects underlined in the review paper are related to the versatility of curcumin showcasing potential therapeutic applications beyond traditional curcumin-therapy. The health-promoting effects of curcumin are well recognized and have been in practice in traditional medicine since ancient times. However, further research is needed to determine the optimal curcumin-based drug dose, bioavailability, and bio-efficacy. The acknowledgment of challenges underscores the need for innovative formulations like nanoparticles to maximize curcumin's therapeutic potential in biomedical applications.

The combination of curcumin with other potential therapeutic reagents should further be explored and tested in controlled clinical studies. While acknowledging the promising therapeutic potential of curcuminoids, we have uncovered potential limitations such as the low bioavailabiliy of the molecule and its fast metabolism, although these present as obstacles, they can be used to our advantage for making different curcumin formulations that are easily metabolized. In summary, our review has uncovered the multifaceted potential of curcumin with multiple benefits and presents itself as an interesting subject for future research.

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Conflict of Interest: Nil

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