Journal of Coastal Life Medicine

journal homepage: www.jclmm.com

Review article https://doi.org/10.12980/jclm.5.2017J7-115

Curcumin – A review on multipotential phytocompound

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ARTICLE INFO

Article history:
Received 11 Jul 2017
Received in revised form 21 Aug, 2nd revised form 4 Sep 2017
Accepted 11 Sep 2017
Available online 26 Sep 2017

Keywords:
Ayurvedic medicine
Turmeric
Pharmacology
Curcumin nano-formulations

ABSTRACT

Curcumin, a polyphenol (diferuloylmethane), is a derivative obtained from the *Curcuma longa*. It has many beneficial functions, including pain-killing, activity against reactive oxygen species, preventing inflammation and antibacterial activities, for which it has been used for centuries in Ayurvedic medication. The mechanisms showing curcumin activity involve a grouping of signaling pathways in the cell at multiple stages. Recently, the anticancer effects of curcumin were studied on different pathways, including the gene expression for cancer, its spread, the regulation of cell cycle, programmed cell death, and tumor expression. All these studies suggest enormous potential of curcumin in cancer therapy. It has many more potential benefits against cardiovascular diseases, reactive oxygen species, bacteria and fungi. The present review provides a brief description of the studies conducted and the information supportive to pharmaceutical activities of curcumin. It also considers anticancer applications and clinical benefits of nano-formulations of curcumin.

1. Introduction

Curcumin, a turmeric pigment, is one of the few promising natural products that has been explored by scientists from both abiological and biochemical point of view[1]. It is the major derivative of the turmeric spice commonly used in India[2]. It is a hydrophobic natural polyphenolic phyto-constituent obtained from the rhizomes of *Curcuma longa* Linn. (Zingiberaceae) (*C. longa*)[3]. *C. longa*, commonly called haldi is basically an Indian spice. It is a medicinal plant known to be used for various ailments since ancient times.

Many studies discuss the degradation and metabolism of curcumin through products and their mechanism of formation[4]. For periods of time, many plants and their derivatives have been used in controlling human diseases as plants contain original components with various beneficial effects[5]. Over more than four decades of scientific research confirmed the various pharmacological effects of curcumin and recognized its ability both as a chemo-preventive agent and possible therapeutic agent against several chronic diseases[6,7]. Current investigations are trying to find out its therapeutic effects against viruses, bacteria, fungi, cancer, inflammation and reactive oxygen species; even still, it is being used to find out various treatments against diabetes, atherosclerosis, asthma, allergies, arthritis, neurodegenerative diseases and cancer[8].

Its mechanisms of action have been explored by many scientists and from these studies, it is clear that curcumin could be well taken at higher concentrations without any toxic effects. Much scientific research now provides a thoughtful view of the therapeutic ability of curcumin[9], but the medical use of curcumin is still less effective because of its low bioavailability and the hydrophobic nature of the molecule[10-12].

2. Pharmacological properties

2.1. Anticancer effects of curcumin

Cancer has diverse histological origin. It does not only have specific therapeutic targets but also some molecular markers that are involved in its initiation and progression. Various targets

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The journal implements double-blind peer review practiced by specially invited international editorial board members.

within the cell that have been controlled by curcumin involve the regulation of the survival as well as death of cancerous cells. It is more effective than other anticancer drugs even at lower dosage and regulates biochemical pathways such as transcription and growth factors, inflammatory cytokines and proteins[13].

Approximately 50% natural products and their derivatives, primarily plants, are proven anticancer drugs[14,15]. Curcumin has also shown its efficacy against many disorders of cancer[16]. Evidence has been provided for the treatment of many human cancers, including pancreatic cancer, by its derivative named polyphenol[17,18].

2.2. Antioxidant property of curcumin

Antioxidants obtained from living organisms have been proven to play an important role in human health[19]. One of the products acting as natural antioxidants is curcumin[20]. Antioxidant property of curcumin is regulated by many enzymes like catalase, superoxide dismutase and glutathione peroxide. It shows 10 times more antioxidant activity in comparison to vitamin E. This might be due to the 1.3-diketone system and phenyl ring with methoxy group[21]. Curcumin can inhibit diabetes, heavy metals, and hypertension caused by stress with its antioxidant, chelating and inhibitory effects on the pathways leading to hypertension[22]. Curcumin, with many of its associated complexes, have the ability to prompt glutathione-S-transferase and hinder free radical generation, thus acting as a free radical scavengers and antioxidants, preventing lipid peroxidation[23].The chemical structure of curcuminoids is also accountable for its antioxidant property[9].

Curcumin regulates expression of pro-inflammatory gene by suppressing transcription factor NF-kB activation. Many cytokines (TNF, IL-1, IL-6, IL-8 and chemokines) responsible for causing infection are also decreased by curcumin. Curcumin has been shown to upregulate *Nrf2* gene in irradiated rat brains[24]. Thus, it has the property of regulating antioxidant mechanisms in rats[25].

2.3. Anti-inflammatory activity

Drugs normally used against inflammation such as steroids and nonsteroidal anti-inflammatory drugs are associated with many harmful effects, but curcumin, having a natural origin, is capable of showing effectiveness against inflammation without such harmful effects[26].

Many potential effects against inflammation have been shown by curcumin and other volatile oils. Acute inflammation is prevented by its oral administration as shown in rats with arthritis of Freund's adjuvant induction, while chronic inflammation was cured by cortisone and phenyl butazone. These anti-inflammatory properties were attributed to its ability to inhibit biosynthesis of inflammatory prostaglandins from arachidonic acid and its neutrophilic function during infection. It also counteracts various skin allergic reactions and irritations related to inflammation[26].

Jurenka[9] reviewed mechanisms of curcumin against inflammation. It is involved in the suppression of transcription factor NF-kB which may lead to the initiation of gene products of inflammation. Various inflammatory cytokines (such as TNF, IL-1, IL-6, IL-8) and chemokines are down-regulated by curcumin. For the early stage of zymosan-induced arthritis, oral administration of curcumin may be a useful strategy for its treatment[27].

2.4. Antibacterial and antifungal activity

Various mechanisms of curcumin against pathogenic fungi have been reported where its response changes with the action of pathogen for which it is to be tested. Many bio-conjugates of curcumin, such as 4, 4′-di-O-glycinoyl-curcumin, 4, 4′-di-O-D-alaninoyl-curcumin, curcumin-4, 4′-di-O-β-D gluco-pyranoside and 4, 4′-di-O-acetylcurcumin, were investigated for their antibacterial and antifungal activities in the laboratory and 4, 4′-di-O-glycinoyl-curcumin was found to be more effective than commercially available cefepime (antibacterial drug). These bio-conjugates were found to be more powerful antibacterial and antifungal agents even than curcumin itself, which might be due to their reduced cellular metabolic rate, higher cellular uptake and suitable levels inside the infected cells.

Many studies have shown the antifungal activity of oil extracted from *C. longa*, such as the restoration of intestinal lesions and weight gain in chicks, and disappearance of lesions in 7 days of turmeric treatment in guinea pigs. Similarly, curcumin has been found to be moderately effective against *Plasmodium falciparum* and *Leishmania major*[5]. Curcumin might be beneficial by acting against gut microbiota thus evading the condition for systemic circulation[28]. The gut microbiota also plays a significant part in curcumin metabolism and its bio-transformation because the microbiota is proficient at converting curcumin formulations into a range of catabolites[29].

3. Cardiovascular effects of curcumin

It has been demonstrated that turmeric is involved in lowering the intake of low density lipoproteins and inhibiting accumulation of platelets, thus leading to decreasing levels of cholesterol and triglycerides. It has been demonstrated in rabbits that turmeric administration leads to lower cholesterol and triglycerides as well as lower exposure of low density lipoproteins to lipid peroxidation, which may be due to increased conversion of cholesterol to bile acids in liver and less cholesterol uptake in

intestines. Similarly, reduced aggregation of platelets is due to potentiation of prostacyclin synthesis and thromboxane synthesis inhibition[2]. Several studies investigated the protective effect of curcumin against the oxidative stress in cardiomyocytes[30].

Curcumin can restore the respiratory activity of mitochondria inhibited by lipo-peroxidation, carboxylation of protein and cell apoptosis[31]. The positive effect of curcumin against cardiomyocytes apoptosis in rats has also been reported[32].

4. Toxic effects of curcumin

Major side effects related to curcumin are gastrointestinal infections including diarrhea and nausea, which might be due to the increased levels of alkalinity in serum. However, it was not clear that abnormal blood levels were because of toxicity of curcumin used as treatment or due todisease[33].

5. Curcumin nano-formulations

Water solubility of curcumin could be increased up to 12-fold (from 0.6 mg/mL to 7.4 mg/mL) without any effect on its biological activity[34]. Dose-dependent free radicals scavenging and cytotoxic effects in MCF-7 and HepG2 cancer cells have been shown by ethyl cellulose (monopolymer of curcumin) and ethyl cellulose methyl cellulose (dipolymer) nano-formulations[35]. These particles showed release of curcumin in circulation and increased attachment to the wall of stomach. Curcumin nanoparticles have been produced using high pressure homogenization with five discrete stabilizers[36].

It has been suggested that poly(lactic-*co*-glycolic acid), cellulose, nano-gel, and dendrimer-based curcumin formulations do not show any kind of damage to erythrocytes and there was no occurrence of thrombus[37]. Therefore, nano-curcumin can be developed as safe, effective and targeted therapeutic modality for cancer[38]. By nano-formulations of curcumin, cancer remedies can be improved by reducing dosage and targeted action on tumors, which shows there may be potential for curcumin nano-formulations *in vivo* trails on humans. But the size of curcumin nanoparticles must be regulated from 10 nm to 200 nm for the applications in drug delivery systems and some commercial applications of curcumin nano-formulations such as nano pure, nano edge, nano morph would also be added to drug market[39]. Nanoparticles of curcumin might be promising in cancer treatments by the targeted delivery in tumors.

6. Conclusion

Curcumin ($C_{21}H_{20}O_6$) has promising ability in the improvement of current medicine for the treatment of various diseases. Safety regarding the use of curcumin make it more interesting since people in India use it orally to cure sore throat. Curcumin has much higher potential of not only the treatment but also the prevention of many diseases as demonstrated by numerous studies. Curcuminoids or derivatives of curcumin are important anticancer and anti-inflammatory agents. However, more studies are required regarding curcumin nano-formulations to find out the effectiveness as well as toxic effects of these particles in small and large concentrations and during different phases of clinical trials. From these studies, it would be possible to compare efficacy of free curcumin and curcumin with its nanoparticles to reveal its effect against cardiovascular diseases and cancer. Most importantly these trials need to be conducted on humans in order to evaluate their effect practically in clinical applications for cancer and other diseases.

Conflict of interest statement

We declare that we have no conflict of interest.

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