Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 5 Issue 2 February 2021

Review Article

A Review on Curcumin and its Medicinal Properties

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Received: December 16, 2020

Published: January 22, 2021

Abstract

Turmeric is a herbal plant (*Curcuma longa*) of the ginger family (*Zingiberaceae*) that has been used traditionally from many years in Asia for medicinal, edible and other purposes. The medicinal properties of turmeric could be allocated to the presence of active components called curcuminoids. Curcumin (60%-70%), demethoxycurcumin (DMC-20%-30%), and bisdemethoxycurcumin (BDMC- 10%-15%) are collectively known as curcuminoids. Many studies conducted in vitro and in vivo in both animals and human beings have recommended that curcumin has strong antioxidant, anti-carcinogenic, anti-inflammatory, anticoagulant, antimutagenic, antidiabetic antimicrobial and many more beneficial properties. Presence of important structural elements: the β-diketone structure, the hydroxyl group at the ortho position in the benzene ring and methoxy groups are highly responsible for the antioxidant activity of curcumin. Presence of important structural elements: the β-diketone structure, the hydroxyl group at the ortho position in the benzene ring and methoxy groups are highly responsible for the antioxidant activity of curcumin. Curcumin hinders the activity of growth factor receptors. The anti-inflammatory properties of curcumin are refereed via its impact on cytokines, lipid mediators, eicosanoids and proteolytic enzymes. Curcumin increases the antioxidant enzymes activities such as: superoxide dismutase, catalase, glutathione peroxidase and heme oxygenase-1. These antioxidant activities decrease the level of lipid peroxidation, so reducing the oxidative damage in the tissues. These measures act as the basis for many of its pharmacological and therapeutic properties.

Keywords: Curcumin; *Curcuma longa*; Free Radicals; Curcuminoids; Anti-oxidant; Anti-obesity; Anti-cancer

Introduction

Turmeric is a herbal plant (*Curcuma longa*) of the ginger family (*Zingiberaceae*) having medical benefits. Curcumin (chemical name: diferuloylmethane) is an active, yellow colored component obtained from rhizomes of turmeric, *Curcuma longa* Linn. (family *Zingiberacea*). It is a perennial herb found mostly from tropical and subtropical regions of world. Fat-soluble polyphenolic pigments also called curcuminoids are mainly responsible for yellow color of Curumin. It was originally isolated 200 years ago and its structure was described in 1910. It has a vast history for being used as a medicine in the treatment of many diseases. Curcumin is a non-toxic and non-mutagenic and has many biological properties including anti-inflammatory, anticarcinogenic, antioxidant, anticoagulant, antimutagenic, antidiabetic, antifungal, antibacterial, antiviral, anticoagulant, antiulcer, hypercholesterolemia, hypotensive and cardioprotective [1]. The most important property of Curcumin is that it has no side effects although act as a therapeutic agent [2]. Curcumin is immensely safe even at high doses and it is proved by many human [3] and animal studies [4].

Curcumin has a long history of medicinal use in India and Southeast Asia and for hundreds of years it has been formed an important component of Indian diet. According to World Health Organization (WHO) approximately 80% of the population in developing countries rely on traditionally used medicinal plants for their foremost wellness [5]. Antioxidants serve as natural defence mechanism that is capable of fighting against free radicals. In recent years, natural antioxidants are being used in the treatment of various diseases. Providing precise plants and vegetables having biochemical functions in diet against toxic heavy metals is trending nowadays [6].

Chemical nature

The medicinal properties of turmeric could be allocated to the presence of active components called curcuminoids. Curcumin (60%-70%), demethoxycurcumin (DMC-20%-30%), and bisdemethoxycurcumin (BDMC- 10%-15%) are collectively known as curcuminoids. The most bioactive component: Curcumin (1, 7-bis (4-hydroxy-3methoxyphenyl)-1, 6 heptadiene-3, 5- dione) is also called diferuloylmethane. Curcumin is also called bis-α, β-unsaturated β-diketone based on its molecular structure. Further, NMR studies confirmed that Curcumin has keto-enol tautomer forms in solution. The bis-keto form dominates during acidic and neutral conditions, whereas the enol form exists above pH8 [7].

Presence of important structural elements: the β-diketone structure, the hydroxyl group at the ortho position in the benzene ring and methoxy groups are highly responsible for the antioxidant activity of curcumin [8]. However, Curcumin decreases the activities of superoxide radicals, nitric oxide radicals and hydrogen peroxide [9]. Other studies reported that curcumin increases the antioxidant enzymes activities such as: superoxide dismutase, catalase, glutathione peroxidase and heme oxygenase-1 (OH-1) [10].

The scavenging and trapping potential of Curcumin can be attributed to their chain breaking activity by donating hydrogen atoms probably from their phenol (OH) groups. Thus, curcumin affords protection against oxidative agents in brain, liver, lungs, kidneys and heart [11].

The Food and Drug administration (FDA) in the USA, the Joint FAO/ WHO Expert Committee on Food additives of the Food and Agriculture Organization/ World Health Organization and the Natural Health Products Directorate of Canada have designated Curcumin and turmeric safe with sufficient tolerability [12]. Remarkably, Curcumin is considered as one of the most mentioned antioxidants because of its various valuable health benefits. Curcumin despite having great health benefits, bioavailability of curcumin is poor with rapid elimination rate. Various natural components have been instigated to improve the bioavailability of curcumin. Piperine is one of them. It is the natural alkaloid of black pepper (*Piper nigrum*), which is a potent inhibitor of biotransformation and especially glucuronidation and it ultimately leads to an increase in the bioavailability of curcumin [13].

Kinetics of curcumin

Previous reports have demonstrated that when rats were given curcumin orally [14] approximately 75% of curcumin is excreted via faeces and only traces of curcumin were observed in urine. However, when curcumin is administered in suspension form of either hepatocyte or microsomal (up to 5 µg/mL), it is excreted within 30 minutes. According to the reports, it was concluded that curcumin was metabolized quickly in the blood after intravenous administration. In mice when curcumin is ingested it is converted into dihydrocurcumin and tetrahydrocurcumin. Later on, these compounds get converted into monoglucuronide conjugates [15]. On the other hand, intraperitoneal injection of curcumin at dose of 0.1g/kg leads to 2.25 µg/mL concentration in the plasma in 15 mins [16]. After 1 hour of intraperitoneal injection, results showed 177.0, 26.1, 26.9, and 7.5 µg/g of curcumin in the intestines, spleen, liver, and kidneys respectively. But in case of brain, just few remains of curcumin (4.1 µg/g) at 1 hour were observed. However, in case of plasma, curcumin, tetrahydrocurcumin and two conjugates of curcumin were detected with the help of HPLC.

Some studies demonstrated that human and rat liver cells were responsible for the bioconversion of curcumin into two main metabolites of curcumin. However, both were not responsible for the inhibition of PGE2 [17]. More often, the bioavailability of curcumin is quite less via oral exposure. The reason for less bioavailability of curcumin might be due to its low absorption in the small intestine, substantial reduction and conjugating metabolism in the hepatocytes and elimination via gall bladder. Moreover, curcumin tends to bind with the enterocyte proteins which can alter its structure can also be the reason of its poor bioavailability [18]. Curcumin binds with serum albumin via hydrophobic interactions [19], and after that it may be shifted to the target cells, where it can perform its pharmacological effects.

Figure 1: Various biological properties of Curcumin.

Various biological properties of Curcumin are discussed as follows in detail (Figure 1).

Anti-viral

It has been reported that curcumin has a broad range of antiviral activity against different viruses: influenza virus, Hepatitis C virus (HCV), papillomavirus virus (HPV), adenovirus, Respiratory syncytial virus (RSV), Hepatitis B virus (HBV), coxsackie virus, Human norovirus (HuNoV) and Herpes simplex 1 (HSV-1) [20]. The antiviral property of curcumin is dependent on dose [21]. Curcumin inhibit activity of inosine-mono phosphate dehydrogenase (IMPDH) enzyme in either non-competitive or competitive manner. By inhibition of IMPDH this led to reduction in the level of intracellular guanine nucleotides which are required for adequate RNA and DNA synthesis. Curcumin mechanism involve in viral entry or other life cycle stages rather than the replication of viral RNA. Therefore, by inhibition of IMPDH, Curcumin have potential anti-proliferative, antiviral and antiparasitic effects [22].

Anti-oxidant

Curcumin is considered as to improve damage caused due to oxidative stress in the body. Antioxidant enzymes repress or check the free radical's generation in cells. Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) serve as the first line of defense against oxidative damage to the cells [23]. Curcumin due to its antioxidant properties, protects the antioxidant enzymes from deterioration by scavenging free radicals and also improves their activity [24]. Acc. to Sharma and Kumari [25] administration of Cadmium chloride to mice generates the oxidative stress in lungs which resulted in elevated lipid peroxidation and declined activity of antioxidant enzymes (SOD, CAT, and GPx). Whereas, Curcumin administration ameliorated the Cadmium chloride induced biochemical changes in lipid peroxidation, SOD, CAT, and GPx activities in lungs of mice which shows the anti-oxidant property of curcumin. Antioxidant enzymes have the abilities to decline nitric oxide formation which is responsible for causing inflammation and carcinogenesis in tissues [26].

Anti-bacterial

Curcumin is also reported to have the ability to hinder growth of a various periodontopathic bacterium and *Porphyromonas gingivitis* Arg and Lys specific proteinase (RGP and KGP, respectively) activities. In relation to this, curcumin also restrained *P. gingivitis* homotypic and *Streptococcus gordonii* biofilm formations in a dose-dependent manner. Curcumin concealed the growth of bacteria completely at very low concentrations. A concentration of 20 µg/mL of curcumin inhibited the formation of biofilm of *P. gingivitis* by more than 80%. However, curcumin did not suppress the growth of Aggregatibacter actinomycetemcomitans even at 100 µg/mL of. Moreover, at proportionately high concentrations, curcumin attacks bacterial membranes (*Escherichia coli*) [27].

Anti-diabetic

Anti-diabetic activity was also reported via Curcumin intake. Antidiabetic activity could be allocated to the antioxidant property of curcumin [28]. Curcumin has the ability to improve the endothelial dysfunction induced due to diabetes by decreasing superoxide generation and vascular protein kinase C inhibition. Curcumin is reported to have the capacity to directly quench reactive oxygen species (ROS) that leads to oxidative stress [29]. Curcumin can lessen cell death due to oxidative stress, indirectly through induction and/or activation of antioxidant (Superoxide dismutase, catalase, glutathione peroxidase)/ cytoprotective enzymes (heme oxygenase-1). These antioxidant enzymes repress or check the free radicals generation in cells which ultimately diminishes the oxidative damage and thus helps protection in diabetic patients [29].

Anti-obesity

Some studies showed that curcumin can improve lipid status as also fat content on treated individuals which leads to the base for studies on obese patients. Some clinical trials result on curcumin demonstrated the anti-obesity effects of curcumin. One study in obese individuals, showed the effect of oral supplementation of curcumin on lipid profile parameters, BMI and glucose levels. The results indicated on significant changes only in triglycerides levels, however other parameters remained unchanged after 30 days-curcumin administration [30].

Anti-allergy/anti-asthma

Curcumin ease the nasal airflow resistance by reducing sneezing, rhinorrhea and nasal congestion. It also represses the IL-4, IL-8, and tumor necrosis factor α as well as also enhanced the levels of IL-10 and soluble intercellular adhesion molecule. Intake of Curcumin via nasal route inhibited inflammations in allergic airway and maintaining structural cohesion in allergic asthma mice. Different doses of curcumin (2.5 and 5.0mg/kg) in ovalbumin (OVA) of Balb/c mice noticeably modulates airway inflammation and airway barrier commonly through modulating cytokine levels (IFN-γ, IL-4, 5 and TNF-α) and sPLA2 activity thereby inhibiting PGD2 release and COX-2 expression. Moreover, curcumin also suppressed the ERK 42/44, p38 MAPK (mitogen-activated protein kinase) and JNK54/56 activation in asthma progression rats [31].

Anti-inflammatory

Curcumin is observed to show significant anti-inflammatory activity in acute as well as in chronic models of inflammation. Curcumin shows its anti-inflammatory activity might be due to regulation of different molecules like transcription factors, cytokines,

protein kinases, adhesion molecules, redox status and enzymes that are responsible for causing inflammation [32]. Tumor necrosis factor α (TNF-α) is a major paracrine and endocrine mediator of inflammation in most diseases/immune functions, and this effect of TNF- α is regulated by the activation of a transcription factor, nuclear factor (NF)- κB. In addition to TNF-α, NF-κB is also stimulated by most inflammatory cytokines, gram negative bacteria, various disease-causing viruses, environmental pollutants, chemical, physical, mechanical, and psychological stress, ultraviolet radiation, cigarette smoke, and many other harmful factors causing diseases. Panahi., *et al.* [33] observed that curcumin has been shown to downregulate activation of NF-κB and NF-κB–regulated gene products which are caused by many disease-causing agents.

Anti-carcinogenic

Carcinogenesis is known to have three separate but interrelated stages, initiation, promotion and progression. Oxidative and inflammatory damage to tissue affects the promotion of cancer [34]. As curcumin is considered as effective anti-inflammatory and antioxidant agent, it may prevent cancer by suppressing the progression of tumour. Curcumin also diminishes the growth and induces apoptosis in different types of cell, as in case of human bladder cancer cells [35]. However, the strongly inhibitory actions of curcumin on several cytochrome P-450s, phenol sulpho-transferase and glutathione S-transferases may be a factor in its anticarcinogenic action [36]. Angiogenesis is known for the formation of new blood vessels from a pre-existing vascular network which is a critical mechanism which may also lead to cancer and atherosclerosis like serious conditions. According to many studies, it was observed that curcumin has an antiangiogenic action that is regulated at the molecular level, by inhibition of vascular endothelial growth factor (VEGF), angiopoiteins (Ang 1 and Ang 2), and inhibition of fibroblast growth factors (bFGF)– induced angiogenesis (reviewed by Dulak [37]). Bone inflammation and cancer are diseases that increase bone resorption. Curcumin is known to stimulate cell apoptosis and to inhibit bone resorption. Therefore, its use has been advocated in cases of bone inflammation and cancer which shows anti-carcinogenic activity of curcumin [38].

Eye disease

Beneficial effects of curcumin have also been reported in some ophthalmological disorders indicating high efficacy of this compound, when applied locally or systemically, orally. It has been demonstrated that putting eye drops for 15-days containing turmeric can boost symptoms occurred due to conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula) and of postoperative cataract patients [39]. With oral intake of curcumin for 12 weeks in the patients with uveitis showed a remarkable reduction in the signs in all treated patients [40].

Wound healing

Wound healing activity by curcumin has also been reported by many researchers. Curcumin can recover the dermal wound healing in normal and diabetic rats via intensifying synthesis of collagen, granulation tissue formation, restoration and biosynthesis of extracellular matrix proteins and TGF-B1. The ability of curcumin to enhance wound healing was utilized by generating collagen films [41]. More recently, a beneficial effect was reported of curcumin in radiation-impaired healing of excisional wounds in mice [42].

Toxicological properties of curcumin

In India consumption of curcumin through ingestion is approximately 80-200 mg/day [43]. The most important property of Curcumin is that it has no side effects although act as a therapeutic agent [1]. Curcumin is immensely safe even at high doses and it is proved by many human and animal studies [43]. According to some researchers, no negative effects were observed in 25 human volunteers who were exposed to 8000 mg of curcumin/day for 3 months. Similar results were observed in 5 more clinical trials where the humans were administered 2000-2500 mg curcumin/day [44]. In India, women used to apply turmeric in order to lessen undesirable hair growth as well as for the treatment of skin and mucous membrane cancers. However, some women encountered with mild dermatitis and itching scalp respectively [45].

According to American Herbal Association, turmeric may act as stimulant of menstrual cycle, in that case it is advisable not to consume turmeric during pregnancy and breast feeding according to some studies [46]. In children, who uses transferable picture tattoos, curcumin was identified as one of the eleven colours. But limited allergic reaction was reported in that case [47].

Conclusion

Curcumin has been used globally for its complete benefits on health. When curcumin is combined with agents such as, carbohydrates, piperine, it gives best of its benefits on health. Because these biological agents significantly increase its bioavailability. Various studies demonstrated that the curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, anti-inflammatory, anxiety and anti-diabetic, hyperlipidaemia. It may also help in the versatile use in Pharmacological industries. Curcumin under certain conditions can also display prooxidant activity as it can induce activation of phase II detoxifying or antioxidant genes representing an important defense against oxidative and electrophilic insults. Thus, Curcumin is potent naturally occurring compound which can be utilized for prevention and treatment of oxidative stress other multifarious diseases such as cancer.

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