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Use of Curcumin in Eye Pathologies: A Review

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ABSTRACT

Curcumin, the main phenolic component of the of Curcuma longa L. root has been shown to possess a high antioxidant activity, anti-inflammatory, anticoagulant, antihypertensive, anti-diabetic, cholesterol-lowering, neuroprotective, hepato-protective, anti-tumor. Experimental studies have highlighted the mechanism of Curcumin action on the regulation of peroxisome proliferation receptors, which play an important role in the regulation of lipid metabolism, in the differentiation of adipocytes and insulin action. Moreover, Curcumin is able to inhibit in vitro COX1 and COX2 enzymes involved in inflammatory reactions and in arthrosis. Inflammation plays an important role in the development of most diseases, especially in ocular pathologies as evidenced by the clinical results obtained in retinitis pigmentosa, cataract, glaucoma, allergic conjunctivitis. The American Food and Drug Administration classifies Curcumin as a substance GRAS (Generally Recognized As Safe), as it is not teratogenic and free of side effects. Only in special cases, such as for pregnant women, people with bleeding disorders and subjects with gallstones, it is necessary to restrict the use.

INTRODUCTION

Curcuma is a spice that constitutes the main ingredient of curry and, in addition to the strong taste and he inviting color, it also has amazing properties. Only recently, Curcuma, also known as the Indian Saffron, has become popular as a spice in the West. In the kitchen and in the Oriental medicine it has been always very important for its food and health properties, so much it to be considered a symbol of prosperity and purifying remedy for the whole body.

Originally India and Nepal, Curcuma longa is part of the Zingiberaceae family and is a shrub plant, evergreen and perennial that can reach the meter of height and the pulverized rhizome is used directly as a spice. The raw extract of the dried and ground rhizome is used as a coloring agent in the kitchen and is cataloged with the initials “E100” with the specific designation of “Turmeric”. The Curcumin as a principal isolated compound it is used, always in the field of food with the symbol“E100” in the list of coloring additives accepted in the food and pharmaceutical sector, it being devoid of toxicity, with the designation of the "Curcumin"[1].

In India, it is used for at least 6000 years, like medicine, cosmetic, spice and dye: for 2000 years the tunics of Buddhist monks were dyed with this root. For the Indians, it is a symbol of prosperity and a means of purification for the whole body. Ayurvedic medicine attributes many of its properties, many of which are confirmed by modern science.

Chemical composition and pharmacological activity

Phenolic compounds called curcuminoids have been found in Turmeric, while the Curcumin is a mixture of three curcuminoids: the actual Curcumin compound, also known as diferuloylmethane, of molecular formula ($C_{21}H_{20}O_6$), is the compound with two methoxyl groups, while dimetossicurcumin and bis-dimetossicurcumina are normally present in lesser quantity. There are also sesquiterpenic substances responsible for the aroma of the spice.

Historically used for digestive problems, dysentery and liver disorders has, in fact, the ability to stimulate biliary secretion by favoring digestion, to fight protozoa and infecting fungi in the intestine; to protect liver tissues, especially when subjected to aggressive drugs or alcohol. It has antioxidant properties, it helps to reduce blood cholesterol and to prevent the formation of emboli by decreasing the risk of heart attacks. Recent studies have shown that Curcumin exerts anti-cancer effects resulting from its ability to induce apoptosis in cancer cells without cytotoxic effects on healthy ones; it can interfere with the activity of the transcription factor α and β TNF (tumor necrosis factor) which has been linked to a series of inflammatory diseases and tumor diseases[2-5]. This tuber also has antidepressive properties: in particular, it is investigating the effect that curcuminoids play on the central nervous system in the regulation of two important neurotransmitters, such as serotonin and dopamine, involved in the modulation of emotional states [6-8].

Due to the poor absorption of Curcumin, being a lipophilic substance the bioavailability is low; recent studies have shown that it can be increased with the simultaneous oral administration of piperine, present in black pepper, which inhibits conjugation with glucuronic acid, avoiding its elimination [9]. Studies have also been carried out on the oral transmucosal transmission of Curcumin; it is deposited in the form of granules in the sublingual area, obtaining a better bioavailability for prolonged contact with the oral mucosa and for direct absorption into the blood flow, avoiding to be rapidly metabolized.

Curcumin presents antibacterial activity and is used not only to prevent the deterioration of food but also for the treatment of small wounds to prevent infections and facilitate the reconstruction of tissues and especially for the protection of skin against damage caused by antitumor radiotherapy [10].

Several studies have shown that Curcumin is not toxic to humans up to 8000 mg for day, but has an important undesirable effect: Curcumin stimulates the formation of singlet oxygen and reduced forms of molecular oxygen in certain conditions of cellular development, and these substances are the cause of the cutaneous photo-toxicity of this plant, it which manifests it with redness of the skin accompanied by burning and itching.

Many articles have also been published for ocular diseases, signaling the efficacy of Curcumin as integrative therapy, mainly related its anti-inflammatory and anti-angiogenic characteristics. In the field of ophthalmology, the first results of its activity were published in uveitis, dry eye, serous chorium retinopathy, diabetic retinopathy and wet macular degeneration both on man or in animal models [11-13]. The relationship between oxidative stress and cataract formation, eye disturbance in which the transparency of the lens of the eye, the crystalline is lost, is highlighted.

Free radicals play a fundamental role in the formation of cataracts: the superoxide O_2- anion, the hydrogen peroxide H_2O_2, the nitric oxide NO and the OH-, hydroxyl radical, acting on the proteins and lipids that make up the biological membranes with a reaction of peroxidation, damaging the membranes and inducing the inflammatory process [14]. In the crystalline, there are three different proteins that can aggregate forming filaments, with degeneration of their original structure, consequent precipitation and loss of the transparency of the lens. The major risk factor is related to advanced age and the only effective treatment is the substitution of the crystalline by surgical intervention.

Retinitis pigmentosa is characterized by degeneration and apoptosis of photoreceptors and pigmented retinal epithelium and there are currently no effective treatments for this disease; Curcumin has shown neuroprotective effect both on a rat and pig model, hoping for its use in the treatment of this pathology. The number of apoptotic cells in the retina of mice decreased significantly and the visual function has been improved; activation of microglia and secretion of chemokines and matrix metalloproteinases in the retina were inhibited after intravitreal Curcumin injection.

Curcumin has also been studied in neurodegenerative diseases such as Alzheimer's, in which the fibrillar β-amyloid aggregates occupy the extracellular space of certain brain zones[15-17]; Curcumin, for its lipophilic nature, is able to cross the blood-brain barrier and bind to the peptide with good results in the improvement of cognitive faculties, in the recovery of memory, with decrease amyloid plaques in the brain, responsible for these effects, because of its anti-inflammatory and antioxidant properties [18].

Curcumin has shown the ability to prevent the formation of cataracts, retinitis pigmentosa, formation of amyloid plaques, acting on free radicals, protecting the biological membranes from the peroxidation [19]. A great limitation of its use, however, is determined by its low bioavailability due to the low water solubility. Current trends in Curcumin research are focused on the development of potential release systems, such as the nanocarrier delivery system, to increase the aqueous solubility, stability, and bioavailability, to achieve targeted action and circumscribed on some target tissues.

Curcumin nanocarrier

The anti-inflammatory, antioxidant and antitumoral properties of Curcumin are due to different cellular mechanisms: this substance produces different responses in the various types of cells which, because of its low availability orally, they are hardly explainable. The main complication to the clinical diffusion of Curcumin is represented by its low gastrointestinal absorption and rapid hepatic and intestinal metabolism. In order to improve absorption, formulations have been proposed with piperine, phospholipids, with other natural components from the essential oil of turmeric or with flavonoids, but while increasing the concentration of adsorbed, the retention of Curcumin in the blood lasted at most eight hours. In addition, several in vitro experiments have shown the possible role of Curcumin in the treatment of common ophthalmologic conditions, such as dry eye syndrome and proliferative vitreoretinopathy, diabetic retinopathy [20]. In ophthalmic therapy, Curcumin administered orally to mice, showed very low concentrations, 0.002%, antioxidant and antiglycine effects through the inhibition of lipid peroxidation. A standardized aqueous extract of Curcuma longa administered topical to rats affected by Escherichia coli- induced uveitis, has greatly reduced inflammation by reducing the activity $\alpha-$TNF [21]. In the literature, it is also reported the preparation of an eye drops in which the Curcumin is stabilized by complexation with β-cyclodextrin, in order to provide a prolonged release to allow an application once a day in retinitis pigmentosa [22].

Potential strategies are aimed at increasing the oral bioavailability of Curcumin, enhancing stability, reducing intestinal inactivation, preventing metabolism and improving intestinal absorption by inclusion in microemulsions, and liposomal, phytosomal, micellar or polymeric preparations. Liposomes are structures consisting of a double layer of closed phospholipids or cholesterol, containing an aqueous solution in which the drug is incorporated, which can penetrate the cell walls releasing the drug inside [23,24]. In liposomes it is possible to incorporate poorly soluble drugs and allow it to be conveyed in the aqueous medium; some of them have been designed with the aim of allowing the administration of Curcumin intravenously and orally.

Solid lipid nanoparticles are lipid-based release systems that have many advantages due to highly degradable physiological lipids, i.e. greater bioavailability, reproducibility, less use of organic solvents in the preparation and, above all, the protection of phyto compounds or drugs, both hydrophilic or hydrophobic, easy sterilization and a long the period of preservation.

These advantages have made the solid lipid nanoparticles suitable for oral administration of various phyto-bioactive compounds, such as Curcumin [25,26]. The superficial modification of these particles with polymers mucus adhesive such as trimethyl chitosan has increased advantages over other polymers, including less toxicity, greater absorption, and elevated mucoadhesive properties and antimicrobial agents that improve the release of phyto-bioactive compounds and, in particular, have shown greater bioavailability of Curcumin in brain cells [27].

Diabetes increases the risk of corneal abnormalities including recurrent erosions, delayed injury and incomplete healing, ulcers and edema, complications after vitrectomy, laser photocoagulation and corneal surgery. Diabetic keratopathy is currently treated with lubricants and antibiotics, contact lenses, surgeries, however, these measures may be ineffective and inadequate in accelerating re-epithelialization in diabetes, with a danger of infection and irreparable problems of vision [28]. One of the main causes of corneal complications in diabetic patients is it represents a decrease in the corneal sensation following a lack of nutrition by the trigeminal nerve [29]. In recent years, studies have shown that it is possible to reach with intranasal drugs the trigeminal nerve and consequently to cure certain ocular pathologies.

It has been shown that the polymer micelle is one of the most suitable nanotechnologies for transport of hydrophobic drugs, by improving the bioavailability of the drug. A nano micellar formulation of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol and Curcumin was administered intranasally in diabetic mice, with abrasion of the corneal epithelium, to assess the efficacy of the drug in the healing of corneal epithelial wounds, caused by diabetic keratopathy. Intranasal administration of Curcumin nano micellular promotes the healing of the corneal epithelial wound in streptozotocin-induced diabetic mice [30]. The results have shown that intranasal administration of the solution of Curcumin nano micelles promotes both the healing of the corneal epithelial injury and the recovery of corneal sensitivity and corneal nerve density.

In addition, for the treatment of ophthalmic disorders, the topical route of administration is to be considered the preferential way by allowing as self-administration in situ, reducing the risk of side effects and, in the case of Curcumin, overcoming the very low systemic bioavailability. Biodegradable synthetic polymers such as polylactic acid, polyglycolic acid and polylactic-co-glycolic acid of the copolymer are commonly used, in the form of scleral caps, to be applied inside the eye, of small dimensions, well tolerated by the organism, biocompatible and safe for clinical use, with the possibility of modifying the degradation of the polymer in months or years [31,32]. The caps are effective for the treatment of vitreoretinal diseases such as proliferative vitreoretinopathy. Polymers for in situ gelation systems have also been proposed for the release of ocular drugs: the gel is transparent and studies on the erosion of bovine cornea have revealed that these polymers and their combinations do not cause irritation significant where they are generated [33].

Glaucoma is a progressive optic neuropathy that leads to irreversible blindness. The high intraocular pressure s attributed the main cause of vision loss, but although continually controlled by the use of appropriate medication, it does not prevent the progression of glaucoma. Increased concern is determined by the apoptosis of the retinal ganglion cells which has now been identified as an early occurrence in glaucomatous degeneration and the inhibition of this process have been addressed by various therapies. Curcumin nano micelles have shown neuroprotective effects in glaucoma, significantly reducing the loss of retinal ganglion cells and therefore can be used as a neuroprotective therapy in glaucoma and other eye diseases with neuronal pathology [34,35].

CONCLUSIONS

The research in vitro and in vivo has shown that Curcumin can be considered not only as a spice in the food sector but also as an effective candidate for the prevention and treatment of many pathologies, even in the long term and without undesirable side effects. The experimental and clinical data obtained so far indicate that oral supplementation with Curcumin is well tolerated and has been proven to be safe in humans and also solubility, chemical stability, antioxidant activity, and bioavailability have been considerably improved after encapsulation in the nano polymeric nano micelles allowing to reach also very delicate organs like the eye and the brain where to carry out its action.

However, all the mechanisms of action with which Curcumin induces its effects are not yet well known, but many studies have shown its importance as an anti-inflammatory, antibacterial, antioxidant, anti-glycemic and anti-tumor agent. In the future, it will be necessary to focus attention on the clinical application of Curcumin in neurodegenerative diseases, ophthalmic diseases, in diabetes, as many experiments have clarified the potential value of Curcumin in these areas.

Competing interests

The author declares that has no competing interests.

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