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Review Article **Open Access**

Curcumina: Vegetable pigment with pharmacological activities and possible therapeutic applicabilities

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Abstract

This study reported the application of curcumin, a vegetable pigment from *Curcuma longa* that has several proven therapeutic actions such as: antioxidant, anti-inflammatory, antimutagenic, antimicrobial, among others. In addition, the increasing development of curcumin-based formulations such as nanoparticles, liposomes, micelles or phospholipid complexes and even associated with photodynamic therapy has provided more preclinical and clinical testing. Thus, the purpose of this paper is to provide a brief overview of the use and latest pharmacological research on the benefits of curcumin for health.

Keywords: Curcumine; Pharmacological activities; Nanoformulations; *Curcuma longa*

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Introduction

Curcuma longa L., belonging to the Zingiberaceae family, is a perennial herb distributed widely in tropical and subtropical regions of the world [1]. This plant plays an important role and is cultivated in Asian regions for its use as a spice and a pigment in food industry [1,2]. Owing to the extensive applications in food, the chemical constituents of *C. longa* had been investigated, revealing two fundamental types of compounds to be curcuminoids and sesquiterpenes [1,3,4], which showed several biological effects disclosing that *C. longa* used as a food spice possesses

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various functions. During the search for pharmacologically active substances from plants. Because of this, much attention has been given to natural vegetable foods, such as natural spices, since they may be potentially beneficial for human health [1].

The medicinal plants have gained great repercussion in the last decades. Its use has increased in the treatment or prevention of diseases around the world, as in Brazil [5-7] There are many reasons for this increase in demand, such as medical, social, cultural, economic or philosophical reasons, which justify the use of plants as a therapeutic option for a significant part of the population, whether rural or urban [8]. The use of medicinal plants is considered one of the first forms of health care used by the human species and is related to the beginnings of medicine [8,9]. Over the centuries, products of plant origin have provided the basis for the treatment of various diseases, both traditionally and due to the knowledge of the properties of a given plant that is passed from generation to generation, either using plant species as a source of active molecules [9]. Pizziolo et al. [10], justify the growth of phototherapy as a modality of treatment, mainly due to the high cost of industrialized medicines. One of the most interesting components of curcumin oil is curcumin (ETO), comprising of aromatic-tumerones (ar-tumerones), α-turmerones, β-turmerones, α-santalene and aromatic curcumene, also possess significant anti-inflammatory and anti-oxidant properties [11]. The oil is a is a small molecular weight polyphenolic compound and lipophillic in nature, hence insoluble in water and in ether but soluble in ethanol, dimethylsulfoxide, and other organic solvents [12]. The other constituents present are volatile oils including tumerone, atlantone and zingiberone and sugars, proteins and resins [12,13]. According to He et al. [14], *C. longa* has several proven therapeutic actions due to the presence of curcuminoids, such as curcumin, which has several advantages such as: antioxidant [15], anti-inflammatory [16], antimutagenic, antimicrobial and various other properties. Curcumin has poor absorption, rapid metabolism and rapid elimination. Several agents have been introduced to improve the bioavailability of curcumin. The most interesting is piperine, which increases the bioavailability of curcumin by blocking the metabolic pathway of curcumin [17]. Curcumin is available in several forms including capsules, tablets and ointments [18]. Curcumin has been approved by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" (GRAS) [19]. Salt formation is the traditional approach to improving the solubility and bioavailability of insufficiently water-soluble substances. However, for molecules of drugs like curcumin that have no ionizable groups, making salt formation not occur. When the possibility of salt formation is ruled out, one can expect to increase the solubility of the drug, forming several solid forms, such as polymorphs, pseudo-polymorphs (stoichiometric solvates), solid solutions, co-amorphous, eutectic and cocrysal solids. Curcumin is stable at the acidic pH of the stomach [12,20]. This review article aims to elucidate the potential pharmacological activities of curcumin and its applicability in therapeutics, as well as gather recent information on this promising pigment that has been studied around the world.

Botanical Description

Curcuma longa is popularly known as turmeric, saffron, ginger yellow, among others. It is an herbaceous, perennial, deciduous, aromatic species with large leaves, long, invaginating and oblong-lanceolate petioles and yellowish flowers, small, arranged in long tips (Figure 1), the rhizome measures about 10 cm in length and when cropped shows a pronounced red orange surface (Figure 2). It has a pleasant odor and aromatic and spicy taste. Native to India is grown throughout the tropical world [21].

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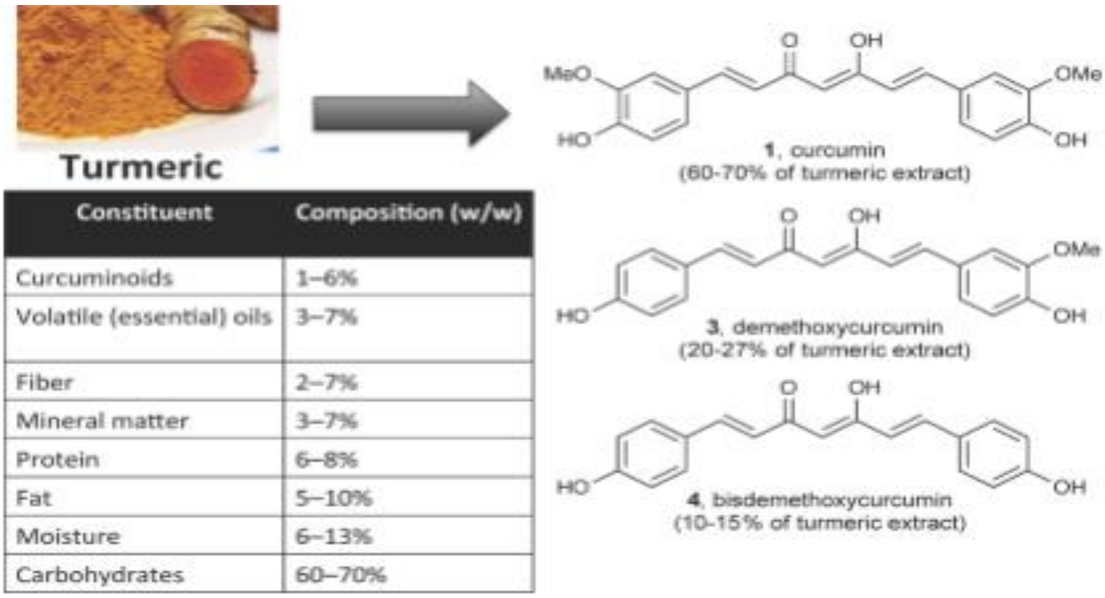
Figure 1: curcumin leaves and curcuma yellowish flowers [8].

Figure 2: Major phytoconstituents of extracts of *Curcuma longa*. Compounds 1, 3, and 4, often grouped together as "curcuminoids", generally make up approximately 1-6% of turmeric by weight. Of a curcuminoid extract, 1 makes up 60-70% by weight, while 3 (20- 27%) and 4 (10-15%) are more minor components [22].



Constituent	Composition (w/w)
Curcuminoids	1–6%
Volatile (essential) oils	3–7%
Fiber	2–7%
Mineral matter	3–7%
Protein	6–8%
Fat	5–10%
Moisture	6–13%
Carbohydrates	60–70%

Chemical structure and Curcumine behavior

In considering potential mechanisms for its range of biological activities, it is important to acknowledge the inherent chemical features of the curcumin molecule. The curcumin is a,-diketone tautomer (Figura 3), 1a, X-ray crystal structure analyses have established that curcumin and its bis acetoxy derivative exist as keto-enol tautomers, 1b, in the solid state. In

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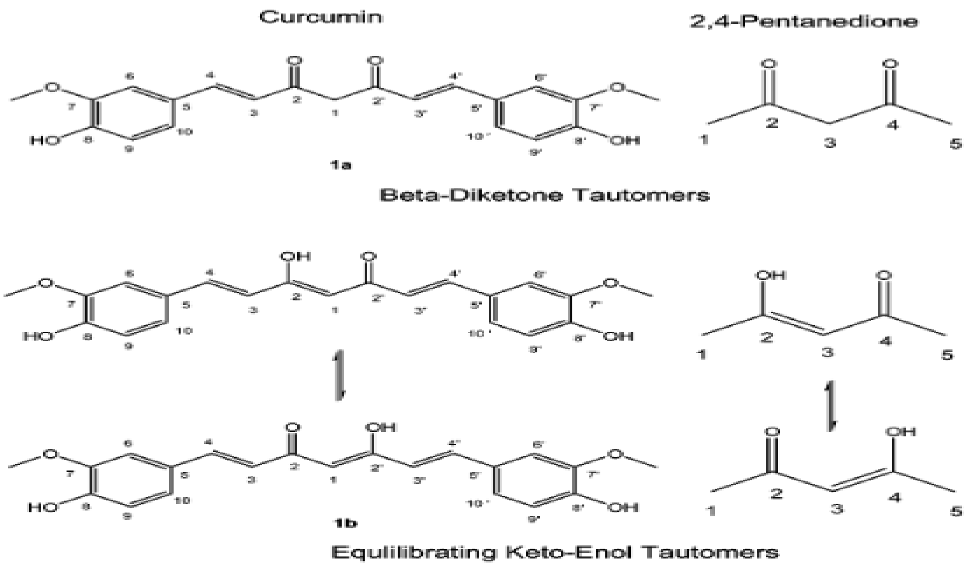
fact, there are three possible structures of curcumin: the,-diketone tautomer, 1a, and two equivalent asymmetric keto-enol tautomers, 1b [23].

Figure 3: Potential solution structures of curcumin and 2,4-pentanedione [23].



Main pharmacological activities and therapeutic applications

Antioxidant activity

Curcumin is available in several forms, including capsules, tablets and ointments. In the scientific milieu and in medicine, reports and effects of curcumin are indicated as the source of future innovative therapies for complex diseases that are believed to require potent but non-selective therapy [22]. Curcumin has demonstrated antioxidant activity with the use of various in vitro antioxidant assays, such as 1,1-diphenyl-2-picryl-hydrazyl (DPPH), 2,2'-azino-bis (3-ethylbenzothiazoline (ABTS) free radical scavenging activity, elimination activity of N, N-dimethyl-p-phenylenediamine dihydrochloride (DMPD) radicals, total antioxidant activity by ferric thiocyanate, determination of total reduction by the method Fe^{3+} Fe^{2+} transformation, superoxide anion radical, riboflavin/methionine system rescue/enlightenment, hydrogen peroxide cleaning and ferrous ion chelating activities (Fe^{2+}) [25].

The antioxidant activity and free radical reactions of curcumin are strongly related to its phenolic structure O-H and C-H. It was analyzed that this antioxidant mechanism of curcumin is based on the H atom abstraction from the phenolic group, and not on the central CH_2 group in heptadiene binding [14]. An effective feature of curcumin for the treatment of Alzheimer's disease is its antioxidant activity which according to Malvajerd, et al [26], experimentally tested lipid nanoparticles demonstrated better optimization of particle size and loading facilitating cerebral abscission of curcumin as a better drug delivery system paving the way for new clinical applications of curcumin in the treatment of SNC.

Photodynamic therapy

According Duse et al. [27], curcumin, is safe for normal cells, has an apoptotic effect on tumor cells after irradiation, exhibiting the ability to

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selectively inhibit tumor growth. However, along with curcumin liposomes, the application of photodynamic therapy could be a promising package to be explored, since the proven hemocompatibilide confers stability and applicability of curcumin-loaded liposomes intravenously at the clinic. The amount of EROs produced by fluorescence indicates that curcumin liposomes caused a maximum damage to tumor cells among the other formulations [27]. The use of curcumin-loaded liposomes together with DNA brings the beneficial properties according Pinnapireddy et al. [28], to improved bioavailability, biocompatibility and transfection efficiency which has been increased in fold. The delivery system and the required dose of irradiation are non-toxic to cells and biocompatible. This multi-component system with photosensitizer and genetic material unites photodynamic therapy with genetics generating new doors in the field of combination for the treatment of cancer.

Antibacterial and antifungal activity

The antibacterial study of curcumin shows the ability to inhibit the growth of a variety of periodontopathic bacteria and specific activities of *Porphyromonas* Arg and Lys proteinase (RGP and KGP, respectively) [29,30] in which curcumin was able to suppress almost total bacterial growth even at low concentrations (20 µg/mL curcumin inhibited *P. gingivitis* biofilms by more than 80% and *Streptococcus gordonii*). From the use of curcumin at minimally inhibitory concentrations, it was observed that there was a similar response to bacterial apoptotic causing reactive oxygen species that led to inhibition of bacterial polymerization resulting in rupture of prokaryotic cell division [12]. The investigation of curcumin mediation for photodynamic therapy can reduce the biofilm biomass of *Candida albicans*, *Candida glabrata* and *Candida tropicalis*. The results demonstrated that the association of four LED influences for light excitation with a concentration of 40 µM curcumin at 18 J/cm^2 inhibited up to 85% of the metabolic activity of *Candida* species tested. The use of curcumin with light has proved to be an effective method for a remarkable improvement in the antifungal activity against the planktonic form of yeasts [31]. The photodynamic effect considerably reduced the viability of *C. albicans* in planktonic or biofilm cultures, probably through increased uptake of curcumin by cells [32].

The considerable antifungal activity of the *C. long* rhizome and its low side effect were the main reasons to investigate its probable synergistic effect with the existing fungicides. The synergistic activity of curcumin with five azole and two polyene drugs including voriconazole, itraconazole, ketoconazole, miconazole, fluconazole, amphotericin B and nystatin showed 10 to 35 fold reductions in MIC values of fungicides versus 21 clinical isolates of *C. albicans*. The synergistic activity of curcumin with amphotericin B and fluconazole may be associated with the accumulation of ROS, which will be suppressed by the addition of an antioxidant [33].

Anticanceric activity

Many studies have pointed out anticancer activities of curcumin alone or in combination with conventional chemotherapy drugs in treatment of cancer and its cancer-related complications. *In vitro* and *in vivo* studies have indicated that curcumin prevents carcinogenesis by affecting two primary processes: Angiogenesis and tumor growth [12,34]. Curcumin has been shown to be effective anticancer activities either alone or in combination with conventional chemotherapeutic drugs. The development of formulations of curcumin in the form of nanoparticles, liposomes, micelles, or phospholipid complexes to enhance its bioavailability and efficacy is still in its early stages [35]. Various nano-sized curcumin

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delivery systems, such as nanoparticles, nanospheres, solid lipid nanoparticles, micelles, and liposomes have been shown to overcome these shortcomings and significantly improve the anticancer and antifungal activities of curcumin. Many studies on curcumin and its nanoformulations are still in the preclinical stage at present [35-37].

Anti-inflammatory and wound healing activity

Curcumin has significant anti-inflammatory activity in both acute and chronic inflammation of acute and chronic inflammation. Curcumin has been shown to be safe in six human trials and has demonstrated anti-inflammatory activity by regulating numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status, and enzymes that have been associated with inflammation [12]. Increased wound healing has been reported by curcumin in animals. The mechanisms of action of curcumin's healing effect include: the immunohistochemical localization of transforming growth factor β1 which has been shown to be more pronounced in wounds treated with curcumin compared to untreated wounds and modulating collagen and decreasing reactive oxygen species promoting thus re-epithelialization [12,38].

Conclusion

From this review article it was possible to analyze the importance of curcumin in innumerable beneficial situations to the organism due to its vast pharmacological activities that can be potentiated synergistically with the association of other drugs or development of formulations that favor the greater uptake of curcumin by the aiding organism in the prevention, cure or palliative treatment of diseases which are of difficult therapeutics. In addition, curcumin due to its natural origin and minimal toxicity alleviates worry about unwanted side effects. Due to this it is necessary to further study this pigment, since its mechanisms of action are still not well elucidated.

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