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Curcumin and its therapeutic uses in oral lesions: A review

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Abstract

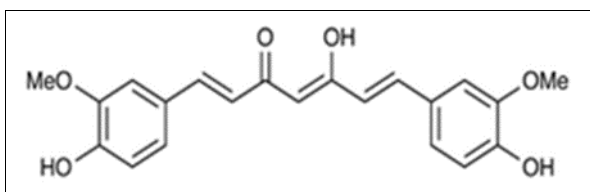
Curcumin is a bioactive component present in the traditional spice turmeric, exists within the perennial plant *Curcuma longa*. Curcumin serves diverse roles across various countries and is presently utilized in a range of forms due to its potential advantages for health. Curcumin's potential also encompasses the management of oral conditions with potential malignancy, such as oral submucous fibrosis (OSMF), oral lichen planus, leukoplakia and radiation induced oral mucositis. The fascination with turmeric's healing possibilities, combined with the relatively straightforward process of extracting curcuminoids, has ignited extensive investigative efforts.

Keywords: Curcumin, therapeutic use, turmeric, premalignant lesions, radiation mucositis

Introduction

Curcumin, a constituent of the traditional spice turmeric, is present in *Curcuma longa*, a perennial plant from the ginger family, known for its rhizomatous growth. Turmeric, sourced from the rhizome, has been a part of traditional Chinese and Indian medicine [1]. With its global recognition, curcumin is now used in various forms due to its potential health benefits [2]. Its historical use is well-documented across approximately 120 different species [3, 4]. Among these, *Curcuma longa* L. (Turmeric) is the most prominent and is cultivated in warm climates worldwide [5]. The interest in turmeric for its therapeutic potential, along with the relatively simple extraction of curcuminoids, has spurred extensive research [6].

The rhizomes, especially the commonly utilized portion, contain a diverse range of compounds [7]. These encompass bioactive non-volatile curcuminoids (curcumin, dimethoxy-, and bisdemethoxy-curcumin), as well as volatile oil compounds like mono and sesquiterpenoids [8, 9]. While the term "curcumin" primarily denotes 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, it is also recognized as "curcumin I." In essence, curcumin is a type of diferuloylmethane exhibiting a crystalline yellow-orange hue. It has a molecular weight of 368.39 g/mol, a melting point of 183 °C, and adheres to the chemical formula C₂₁H₂₀O₆. From a chemical perspective, curcumin demonstrates keto-enol tautomerism, implying that its primary form in neutral and acidic solutions is keto, while the more stable enol form becomes prominent in alkaline solutions and the solid state.



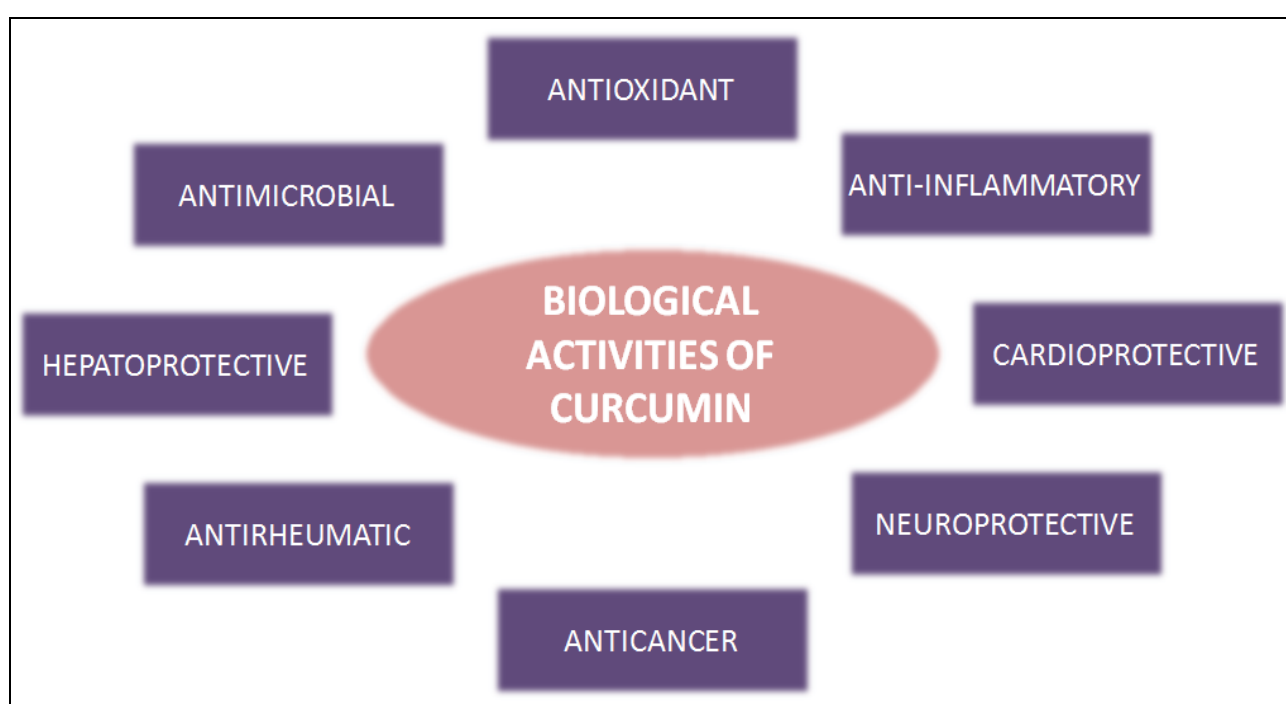
Curcumin-I

There exist two additional compounds referred to as curcumin, namely curcumin II (also known as demethoxycurcumin) and curcumin III (also known as bisdemethoxycurcumin) [11].

For instance, in different countries, turmeric, which contains curcumin, has diverse applications: in India, it's utilized in curries; in Japan, it's served as tea; in Thailand, it's integrated into cosmetics; in China, it serves as a colorant; in Korea, it's found in beverages; in Malaysia, it acts as an antiseptic; in Pakistan, it's employed as an anti-inflammatory agent; and in the United States, it's used in mustard sauce, cheese, butter, and chips, functioning as both a preservative and a coloring agent, apart from being available in capsule and powder forms [2]. In Northern India, postpartum women receive a tonic composed of fresh turmeric paste, dried ginger root powder, and honey, mixed in hot milk to be consumed twice daily. Turmeric poultices are also applied to the perineum to facilitate healing of birth canal lacerations [12]. Powdered turmeric mixed with boiled milk is taken to address coughs and respiratory issues, while roasted turmeric is utilized as a remedy for children with dysentery [13]. This ancient remedy is also employed for treating dental problems, digestive disorders like indigestion and acidity, flatulence, ulcers, and

even counteracting the effects of hallucinogens and psychotropic substances [14]. In the realms of food and manufacturing, curcumin currently serves as a natural yellow colorant and is used in perfumes. It's also an approved food additive for flavoring curries and mustards [1].

Curcuminoids have received the "Generally Recognized As Safe" (GRAS) designation from the US Food and Drug Administration (FDA) and have shown favourable tolerability and safety profiles in clinical trials, even at doses ranging from 4000 to 8000 mg/day [15]. Moreover, doses as high as 12,000 mg/day of a 95% concentration of three curcuminoids—curcumin, bisdemethoxycurcumin, and demethoxycurcumin—have been tested without significant adverse effects [16]. The *Curcuma* species boasts an array of beneficial pharmacological attributes [17–20]. A total of 31 *Curcuma* species have undergone study, with the most extensively examined ones being turmeric (*C. longa*) and zedoary (*Curcuma zedoaria* (Christm.) Roscoe) [4].



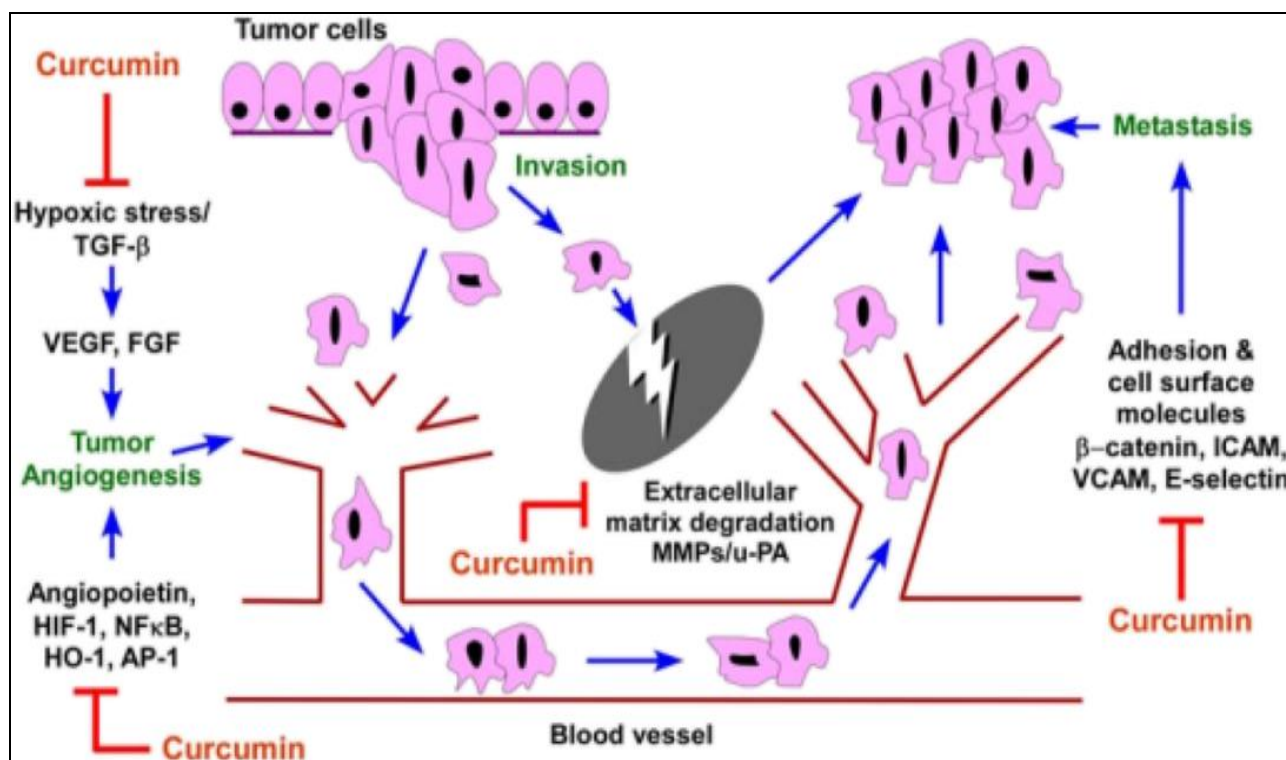
Schematic illustration of curcumin biological activities

Curcumin in oral cancer and oral pre-malignant lesions

The involvement of free radical-induced lipid peroxidation has been observed in various cancer types, including oral cancers. Levels of lipid peroxidation byproducts in saliva such as malonaldehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) have been identified in oral cancer [21]. Research has indicated a connection between increased lipid peroxidation products and decreased antioxidant activity in cancer cases [22, 23]. Clinical trials have demonstrated potential benefits of antioxidant supplementation (such as vitamins C and E) in cancer prevention [24, 25]. Over the past fifty years, extensive investigations have shown that curcumin, a yellow pigment found in turmeric, possesses stronger antioxidant properties compared to α -tocopherol [26]. Curcumin has been associated with the suppression of mutagenesis and has been utilized as a chemopreventive agent against various cancers, including those affecting the colon, breast, prostate, esophagus, lung, oral cavity, as well as in hindering atherosclerosis and

restraining viral and bacterial growth [27].

The effect of curcumin on angiogenesis and metastasis in cancer cells. Studies have demonstrated that curcumin can reduce the activity of NF- κ B and COX-2 induced by substances like STE (khaini) or NNK in oral premalignant and cancerous cells in vitro [28]. Curcumin has the potential to hinder the development of oral pre-cancerous and cancerous conditions by impeding the activity of free radicals [29]. Possessing potent chemopreventive qualities, curcumin exhibits notable antioxidant and therapeutic attributes in various ailments, including cancer and diabetes. It functions as a scavenger of reactive oxygen and nitrogen species, countering their harmful effects. Curcumin (*Himalaya haridra*) in systemic form have been administered to the study population in various investigations for three months, with capsules containing 400 mg of curcumin presenting with potential benefits [30].



Curcumin in radiation induced oral mucositis

Curcumin interferes with inflammatory responses by diminishing the activity of enzymes like cyclooxygenase-2, lipoxygenase, and nitric oxide synthetase. Additionally, it inhibits the generation of inflammatory cytokines such as tumor necrosis factor alpha (TNF- α)^[31-33]. Furthermore, it counteracts the presence of free radicals in tissues and averts their damaging effects^[34]. The compound also plays a protective role against the development of normal cells into cancerous ones. Its antioxidant properties manifest in the inhibition of superoxide radicals, hydrogen peroxide, and nitric oxide. Curcumin has demonstrated its ability to regulate the cellular functions of cytokines as well^[35, 36]. Notably, it has been applied in treating skin issues like itching, acne, eczema, and wrinkles, and has shown effectiveness in wound healing. The utilization of herbal remedies is recommended to proactively prevent injuries induced by radiation therapy and bolster tissue resilience, ultimately mitigating the severity of resulting damage^[37]. Various studies have examined the impact of curcumin on these effects^[38].

Turmeric takes a prominent role in wound healing, as evidenced in multiple studies^[39]. Extensive research supports the efficacy of turmeric and curcumin in addressing potentially malignant conditions like oral submucous fibrosis,⁴⁰ and oral lichen planus^[41]. The utilization of a 0.004% curcumin mouthwash has been found to be well-tolerated and effective in alleviating the signs and symptoms of oral mucositis induced by chemo-radiotherapy^[42]. A turmeric gargle prepared from a 400mg turmeric capsule has shown promise in reducing and delaying the severity of oral mucositis. Curcumin's bioavailability is constrained due to its limited absorption and rapid metabolism and excretion upon oral consumption. To address this challenge, Delavarian *et al.* (2019) introduced an oral curcumin nanomicelle tablet of 80mg/day, which proved effective and safe in preventing and lessening the severity of oral mucositis. This approach also exhibited the potential to mitigate weight loss^[43]. Encapsulating curcumin in nanoparticles enhanced its solubility in aqueous solutions, thereby increasing oral

bioavailability and achieving notable serum and tissue levels, as observed by Shaikh *et al.* (2009)^[44]. These curcumin nanoparticles were also found to be water-miscible^[45]. Another study by Arun *et al.* (2020) reported that a bioavailable turmeric extract capsule of 1500mg/day taken after meals lowered the occurrence and intensity of oral mucositis without causing systemic toxicity, indicating its safety^[46, 47]. Adhvaryu *et al.* (2018) suggested an oral curcumin dose of nearly 2000mg/day combined with piperine to enhance its bioavailability, leading to reduced incidence of grade III and IV mucositis, improved patient compliance, and reduced drop-out rates^[48].

Discussion

Remarkably, this natural polyphenol has gained the moniker of the "wonder drug of life"^[49]. In ancient times, particularly in the Far East, turmeric was utilized to address inflammatory conditions affecting various organs, manage liver and digestive tract issues, and promote wound healing. The 1970s marked the commencement of research into the health benefits of curcumin. Over subsequent studies, curcumin has been demonstrated to possess multifaceted therapeutic potentials^[50-53]. Despite these findings, turmeric has not yet gained widespread recognition as a therapeutic agent on the commercial front^[49]. Its utilization in medical clinics remains infrequent due to its limited bioavailability. The hydrophobic nature of curcumin following oral ingestion contributes to its inadequate absorption through the gastrointestinal (GI) tract. However, curcumin displays a promising potential for therapeutic development derived from turmeric, given its classification as a Generally Recognized as Safe (GRAS) substance, characterized by stable metabolism and minimal toxicity^[54]. Notably, curcumin's role in industrial applications as a coloring agent is also noteworthy^[5, 11].

Recent years have seen the emergence of numerous studies investigating the biological effects of curcumin. With over 3000 recent publications, curcumin has showcased diverse impacts in cancer treatments. Its repertoire includes antioxidant, antibacterial, antifungal, antiviral, anti-

inflammatory, anti-proliferative, and pro-apoptotic effects, among others. Curcumin exhibits remarkable potential in addressing neurodegenerative diseases, arthritis, diabetes, psoriasis, allergies, intestinal inflammation, kidney toxicity, Alzheimer's disease, depression, AIDS, multiple sclerosis, cardiovascular conditions, and most importantly, cancer [55-58].

Conclusion

Curcumin is recognized as a safe and non-toxic compound with a highly promising role in cancer treatment. Its potential extends to the treatment of oral potentially malignant conditions such as oral submucous fibrosis (OSMF), oral lichen planus, and leukoplakia. Curcumin has demonstrated favorable outcomes in addressing these lesions, with noticeable reductions in their size and improvements in mouth opening observed particularly among OSMF patients. Notably, utilizing curcumin presents a cost-effective approach. However, to comprehensively assess curcumin's efficacy and determine the optimal dosage, further research involving a larger population is necessary.

Conflict of Interest

Not available.

Financial Support

Not available.

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