Curcumin: A Brief Review Article

Role of curcumin in management of potentially malignant disorders: A review of literature

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Abstract

Potentially malignant disorders (PMD) are premalignant lesions or conditions having a high rate of malignant transformation. The risk of malignancy accounts for more than 50% in the commonly occurring oral PMD. There is a need to identify oral PMD early on and prevent their transformation into malignancy. Oxidative stress plays a major role in the pathogenesis of oral PMD. Curcumin, an antioxidant has shown promising results in oral PMD by reducing oxidative stress by various mechanisms. The aim of this article is to shed light on the use of curcumin in different oral PMD, its benefits, and shortcomings based on previously published literature.

Introduction

Among all malignancies occurring universally, oral carcinoma accounts for 3%.[1] Potentially malignant disorders (PMD) develop into oral carcinoma. Diagnostic delay in the recognition of manifestation of oral PMD is caused by lack of awareness among the general population and health-care professionals.[1,2]

The World Health Organization defines PMD as a lesion/condition which has a risk of transforming into malignancy either at initial or later diagnosis.[1,3] Leukoplakia, erythroplakia, Lichen planus (LP), and oral submucous fibrosis (OSMF) are the most commonly occurring PMD and most likely to transform into malignancy.

Leukoplakia, a precancerous lesion is a white patch or plaque that cannot be histologically or clinically distinguished as any other disease.[1] Buccal mucosa, lip, and gingiva are the more commonly involved. Lesions occurring in floor, tongue, and Vermilion area have a significant association with dysplastic changes, which is reported to be 15.6-39.2%.[3,4] A study revealed that most of the lesions were mild to moderately dysplastic followed by severely dysplastic/carcinoma *in situ* and straight out carcinoma.[5]

Proliferative verrucous leukoplakia (PVL), a precancerous lesion, is a belligerent form of leukoplakia occurring more commonly in women and with no associated habits. Multifocal white patches with roughened surface projections occurring frequently on gingiva form the clinical consistencies of PVL.[3] According to some authors, chances of PVL transforming into oral carcinoma are more than 60%.[6,7]

Erythroplakia is a velvety bright red plaque that is not clinically or histologically ascribed to any other condition.[1] Clinical features involve a high prevalence in males and occur in the floor of the mouth, tongue, soft palate, and retromolar pad. They are usually asymptomatic but sometimes might be associated with burning sensation.[3,4] According to a study, half of erythroplakia transformed into malignancy, closely followed by carcinoma *in situ* and remaining showed mild to moderate dysplastic changes.[8]

OSMF may be defined as a slowly progressing disease, in which the fibrous bands form in the oral mucosa, ultimately leading to severe restriction of movement of the mouth including the tongue.[8,9] The highest incidence is seen in South East Asians and has been associated with betel nut chewing. This condition is most commonly seen in young adults, in the second to fourth decade of their life. Clinical manifestations include buccal mucosa as the most frequently occurring site and severe trismus and burning sensation as the presenting

complaint.[2,10] In comparison to healthy people, patients with OSMF are 19 times more likely to develop oral carcinoma.[3] According to a recent study, oral carcinoma originating from OSMF occurs at a younger age, is more common in men and is more aggressive and possibly more likely to metastasize than oral carcinoma developing from other origins.[11]

LP is a precancerous chronic mucocutaneous autoimmune condition, affecting middle-aged women. Most involved sites include buccal mucosa tongue, gingiva, palate, and the vermilion. The risk of malignant change in oral LP is reported to <5%.[3,12,13]

In most of the PMD, tobacco has been considered as a major factor in the etiopathology, clinically, or histologically. Diverse oral PMD have been reported in the literature with the consumption of tobacco. PMD are known to be associated with cigarette smoking, excess alcohol consumption, and betel nut chewing. Besides these, immunocompromised conditions such as diabetes and certain dietary factors are independent risk factors for the development of oral PMD. Studies show that human papillomavirus (HPV)-16 and HPV-18 are also considered to be the viral etiopathology of oral PMD.[14-16]

Since oral PMD have a high tendency to transform into malignancy, there is a need to identify these disorders early and prevent their transformation to malignancy by various means.

Pathogenesis of oral PMD is reliant on oxidative stress. Pro-inflammatory external factors such as tobacco chewing, smoking, and stress lead to reactive oxygen species such as free radicals (superoxide anion, hydroxyl, and nitric oxide radical) and lipid peroxides in the body. As a result of oxidative stress, there is increase in cellular glutathione (GSH) levels and stress-induced activation of activator protein-1 (AP-1) and nuclear factor-kappa B (NF-Kappa B). This is due to an imbalance between antioxidant enzymes and free radicals. A normal, healthy cell thus starts converting to a neoplastic cell. DNA damage occurs either directly, or there is an interference with DNA repair via protein damage. To prevent such oxidative damage of DNA, lipid, or proteins, effects of free radical production must be counteracted by an antioxidant mechanism.[17]

Antioxidants are those substances, which will considerably delay or inhibit the oxidation of a substance and protect the body against oxidative impairment. They act by breakage of chain reaction, reducing the concentration of free radicals, scavenging initiating radicals or chelation of transition metal catalyst. Low antioxidant levels cause oxidative imbalance which damage or destruct cells. As oxidative stress appears to be an important part of many diseases, it is both the source and the outcome of disease.[18]

Natural antioxidants include superoxide, hydroxyl peroxide, GSH peroxidase, tocopherols, carotenoids, bilirubin, uric acid, melatonin, lycopene, and ascorbic acid. Butylated hydroxyanisole and propyl gallate are some examples of synthetic antioxidants.

Other antioxidants include curcumin, which is our area of interest. In this paper, authors describe the role of curcumin in prevention and of management PMD and review previous published literature on this subject. Curcumin is diarylheptanoid, belonging to the group of curcuminoids, which are natural phenols responsible for its yellow color. It is a member of the Zingiberaceae family.[19]

Since ancient times, turmeric has been used in South East Asia as a part of culinary recipes and as traditional medication for ailments. It is sold as an herbal supplement, added to cosmetics, used to flavor food, and as a food coloring.

They exhibit antineoplastic, antiproliferative, and antimutagenic activities by subduing initiation, progression, and metastasis and interrupting cell cycle by disrupting mitotic structures and inducing apoptosis.[20]

As discussed earlier, AP-1 and NF-Kappa B have been associated with the pathogenesis of oral PMD; curcumin exerts positive antineoplastic effects by suppressing the activation of these factors. Increasing levels of vitamins C and E, which prevents peroxidation of lipids, damage to DNA are thought to be the antioxidant mechanism of antineoplastic effect of curcumin.[20,21]

Curcumin reduces inflammation and it acts as an antimicrobial and a chemo-radiosensitizing agent and helps in wound healing apart from its antineoplastic properties.[22]

In a descriptive study, authors reviewed the efficacy of commercially available turmeric, by evaluating the treatment outcomes of 30 patients aged 18-50 years in histologically diagnosed OSMF. Visual analog scale (VAS) for pain was used to evaluate burning sensation, and maximal incisal opening was recorded for mouth opening. Based on measurements, they were classified into 4 groups. All four groups were administered with turmeric tablet of 300 mg curcumin and 5 mg piperine. They observed that there was a significant decrease in burning sensation in these patients but found no considerable increase in mouth opening.[23]

An observational study to evaluate the clinical efficacy of curcumin for the OSMF management was carried out in 41 patients aged 17-56 years. They were given various combinations of curcumin, which was to be applied 3-4 times a day. Blood samples to review any systemic changes due to medications, along with burning sensation and mouth opening were collected before and following treatment. Follow-up was on a monthly basis for first 3 months. Improvement in burning sensation and mouth opening following treatment was statistically significant. Authors concluded that turmeric offered a safe and efficacious symptomatic treatment option of OSMF.[24]

Efficacy of curcumin as a chemo-preventive agent was assessed in a comparative study in 48 patients with histopathogically diagnosed OSMF. They were divided into three groups, in which one group received curcumin capsules, the second group received turmeric oil, and the control group received placebo tablets. Follow-up was done every 2 weeks for first 3 months during treatment and monthly once for the 6-month following treatment. The author noticed a significant improvement in the clinical manifestation of the condition, and the results were almost equal by use of either of the form of curcumin. Positive histopathological changes were noted following treatment.[25]

Curcumin efficacy in precancerous lesions was evaluated in 75 patients in a prospective study. 25 patients each having leukoplakia, OSMF, and LP were given 1 g of curcumin tablets

containing 900 mg of curcumin, 80 mg desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin. Pain control and resolution of the lesion were the main clinical criteria used for assessing changes in oral leukoplakia and LP. Pain was evaluated on VAS and for healing, changes in lesion size included ulcer size from baseline, while in OSMF, change in mouth opening was considered. Along with this, collection of serum and salivary samples was done. Whole unstimulated saliva produced in a 5-min period (about 3 ml) was collected along with blood samples. Blood was centrifuged at 1700× *g* for 10 min and plasma was separated. Curcumin improved the clinical symptoms and reduced the lesion size in all patients. Curcumin increased the local level of vitamin C and E, while it decreased DNA damage and peroxidation of lipids for the patient suffering from precancerous lesions, which was suggestive of antiprecancerous effect through antioxidant pathways.[25]

A double-blind, randomized, placebo-controlled trial was conducted in 20 patients with oral LP. A numerical rating scale was used to quantify the symptoms, and a modified oral mucositis index was used to measure the signs of erythema and ulceration. Curcumin at doses of 6000 mg per day in 3 divided doses showed a great reduction in the manifestation of the disease in the case group as opposed to control group.[26]

Authors successfully encapsulated curcumin into nanoparticles. The nanosystem maintained the stability of curcumin against degradation in phosphate buffer mucin in an attempt to mimic the salivary physiological condition. Furthermore, it showed preferential mucosal uptake. Efficacy of curcumin in such form was evaluated in 10 patients suffering from erythroplakia. Pain index and the lesion size measurement were considered as the clinical criteria. The gel in a dose of (6 mg/day) showed a pronounced effective pain index and reduction in the lesion size. Moreover, disappearance of the lesions, after 6-week course topical curcumin treatment was observed. A larger sample size and randomization were required to further reckon the success of these nanoparticles.[27]

A study conducted in 10 patients with histologically diagnosed LP, curcumin was used as a treatment option for intraoral lesions. Topical application was preferred twice daily for a period of 3 months. Encouraging results were found both in terms of symptomatic relief and significant decrease in the size of the lesion.[28]

India produces nearly the whole of the world's turmeric crop and consumes 80% of it.[29] Curcumin is available in oral, intravenous, subcutaneous, and topical application in the form of gel, ointments, and nasal spray. There are certain limitations of using curcumin commercially like low solubility, prompt breakdown, and rapid elimination; hence, less than required bioavailability.

Recent developments in the field of buccal drug delivery show an increased interest toward nano buccal drug delivery techniques to provide a superior alternative in terms of enhanced localization and drug targeting. Curcumin being highly hydrophobic can be benefited by this system. Drawbacks of poor aqueous solubility are evaded. The nanosystem includes liposomes, micelles, and phospholipids that improve gastrointestinal absorption of curcumin, thereby providing higher plasma curcumin levels and reduced elimination resulting in improved bioavailability. Better permeability and resistance to metabolism can be achieved by use of adjuvants with curcumin.[19]

Conclusion

There are numerous research papers published in the literature, which suggest the protective role of curcumin in the prevention of precancer. Curcumin is safe, non-toxic, and effective. It is an economical alternative used in oral infection and periodontal diseases. Development in targeted drug delivery such as nanoparticles loaded with curcumin seems to be very promising in enhancing its efficacy. Further research is needed to determine the long-term effects of curcumin and its outcome on a larger sample size. There is also need to understand the dosages and physical form of administration in the application of curcumin to the desired lesion in the oral cavity. More randomized controlled trials and meta-analysis of data would further shed light on the benefits of curcumin in oral PMD.

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