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A Gift of Mother Nature – Curcumin an Alternative Chemo-Preventive Drug

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ABSTRACT

India is the world capital for Oral cancer. The chemo preventive actions of many natural compounds were known to our fore-fathers in prehistoric era. These natural compounds are potent, less toxic and have greater biocompatibility. Natural compounds have been extensively studied over decades for various diseases including cancers. Curcumin is one of the important natural chemo preventive drug used for various cancers. It plays very important role in apoptosis, reduction of inflammation in tumour microenvironment. In this article we tried to elucidate the action of "Curcumin" in OSCC and potentially malignant disorders. Here we highlight Curcumin can be a promising therapeutic drug.

Keywords: Curcumin, natural compounds, Chemoprevention, OSCC.

INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) is one of the sixth most important common cancer, with an annual incidence of 36.2 million and approximately 8.2 million deaths per year all over the world. OSCC is a major public health concern due to increasing trend in incidence, increasing number of cases occurring in younger age group and its occurrence in patients without tobacco habit [1].OSCC has higher predilection for males with the incidence rate of 5.5 among men and 2.5 in women for 1, 00,000 populations [2].Among males and females 64,225 and 33,668 respectively, new oral cases were reported in 2011. The number of cases is expected to increase exponentially to 100,389 among males and 54,458 cases among females by 2026[3]. However the annual incidence rate of oral cancer is 12.6 per 100,000 population with death rate of about 2000/day[4].The GLOBOCAN has predicted that India's oral cancer burden will be around 1·7million by 2035 and number of cancer

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deaths will also rise to 1·2 million in the same period [5]. The tobacco habit either chewing or smoking is common etiologic factor and alcohol habit is the co-factor. Most of the Oral cancers are preceded by clinically detectable potentially malignant disorders[6]. The most common cancer site is Buccal mucosa followed by tongue [7-8]. Even with the advent of medical field and enormous scientific research, no specific treatment is available for potentially malignant disorders. Interestingly, despite of multimodal treatments like Surgery, Chemotherapy, and radiotherapy, no improvement in the prognosis of OSCC patients, causing high mortality rate and severe chemo/radiotherapy related morbidity in survivors. Research on new chemo preventive and therapeutic drugs with lesser toxicity is a need of hour.

India has a rich treasure of medicinal plants and its knowledge goes back to 600BCE, the details were given in Sushrutha Samhita written by Sage Sushrutha an ancient Indian Physician. For decade's scientific knowledge of various medicinal plants have been elucidated and has been extensively used as a therapeutic agent for un-curable diseases such as cancer.

Curcumin (diferuloylmethane) is considered as most important and chief component of common Indian spice turmeric and is derived from the rhizome of the plant *Curcuma longa*. *Curcuma longa, a* perennial plant, belonging to member of the Zingiberacae (ginger) family [9]. Curcumin is the principal curcuminoid accounting for approximately 2-5% of turmeric.

Curcumin can play major role as a chemo preventive drug to treat various oral potentially malignant disorders, but literature on its efficacy is very minimum [10]. In a clinical trial by Cheng AL*et al*, found that the curcumin was nontoxic even at the dose of 8000mg/day for 3 months. They found histologic improvement in 2 out of 7 oral leukoplakia patients. But even at high dosage, malignant transformation was seen in 1 out of 7 patients[11].Free radicle mediated lipid peroxidation and low antioxidant levels play an important role in carcinogenesis. After the dose of 1g of curcumin for 9 months, significant reduction in the lipid peroxidation products (malonaldehyde (MDA) and 8-hydroxydeoxyguanosine) was noticed in saliva. Similarly increase in antioxidant vitamins C and E, provide potent anticancer effect by preventing free radicle mediated lipid peroxidation and DNA damage inpotentially malignant disorders [12]. A multicentric clinical trial was done on oral leukoplakia (n = 223), dose was 3.6 g/day for 6 months. Clinical response was observed in 67.5% patients, 88.9% subjects showed complete response, demonstrating that there was no relapse after 6 months follow-up. Hence the difference in histologic response between Curcumin and placebo was found not significant. However, when combined with clinical and histological response assessment indicated a significantly better response to Curcumin but continued treatment in partial responsive patients did not yield any additional benefit[13].

Areca-nut chewing causes the overexpression of Connective tissue growth factor (CTGF) resulting in enhanced fibrotic activity. Curcumin completely inhibited arecoline-induced CTGF synthesis in cell lines and the inhibition was dose-dependent [14].Curcumin inhibits the proliferation of fibroblasts and as well as myofibroblasts which decreases the generation of collagen type I and III in myofibroblasts. It helps in inducing apoptosis in myofibroblasts by down-regulating the Bcl-2/ Bax ratio [15]. Significant reduction in the expression of p53, iNOS, and TGF-â was noticed after treating OSF patients with Curcumin 300mg/day for 9 months[16]. At the dose of 600mg/day for 3 months clinically significant reduction in burning sensation as well as marginal improvement in other clinical features was noticed in OSF patients[17].Trial on Curcumin lozanges for three months showed significant improvement in clinical symptoms and sustenance when compared to controls, which showed relapse of symptoms within 6 months of follow up [18]. Chainani-Wu *et al* studied on Curcumin and found that no clinical improvement in the oral lichen planus at the dose of 2000mg/day [19]. However they showed significant clinical improvement with the dose of 6000mg/day for 14 days. They also found reduction in CRP and IL-6 at the end of 2 weeks proving anti-inflammatory effect of Curcumin [20].

Curcumin has very minimum effects on the growth of normal oral epithelial cells (NOM9). In the immortalized, leukoplakia, and cancer cells,

curcumin inhibited cap-dependent translation by suppressing the phosphorylation of 4E-BP1, eIF4G, eIF4B, and Mnk1, and also reduced the total levels of eIF4E and Mnk1 resulting in suppression of tumour growth and disease progression [21]. 10μM Curcumin is significantly inhibited arecoline-induced ERK activation and completely blocked arecoline-induced Placenta growth factor (PlGF) mRNA expression, probably by preventing the generation ROS [22]. In the presence of copper, curcumin treated OSCC cell lines showed increased level of Nrf2, induction of intracellular ROS and early apoptosis. In these cells suppression of epithelial-mesenchymal transition and migration was noticed. It is well known fact that in OSF the tissue copper content is higher compared to normal. This property can be added advantage in treating OSF or OSCC in OSF patients [23].

Curcumin treated SCC-25 cell lines had decreased expression in MMP-2 and MMP-9, also modulated the expression of various EMT markers, such as Snail, Twist, and E-cadherin, and induced p53 expression that is crucial to EMT repression [24]. Curcumin reduced SCC-25 cells proliferation and invasion through inhibiting the phosphorylation of EGFR and EGFR downstream signalling molecules Akt, ERK1/2 and STAT3. It also inhibited SCC-25 cells invasion and down regulated MMP-2, MMP-9, uPA and uPAR expression [25]. Curcumin when treated SCC-25 cell lines co-cultured with carcinoma-associated fibroblasts showed decreased release of EMT-mediators in CAFs and reversal of EMT in tumor cells resulting in decreased invasion. In tumour cells, the levels of nuclear factor κB (NFκBα) and early response kinase (ERK) were decreased and in fibroblasts, integrin αv protein synthesis was decreased compared to corresponding cells in normal co-culture. [26-27]. Curcumin suppresses NF-KB by inhibiting IK (inhibitor kappa B kinase) via an AKT-independent mechanism, resulting in blockade phosphorylation of IkB-á, causing NFkB sequestration in the cytoplasm [28].

Curcumin selectively suppresses the transcription of HPV16/E6 oncogene in HPV16-positive cell line 93VU147T. It also inhibits the activity of host nuclear transcription factors AP-1 and NF-kB. [29].Curcumin used with either 5-FU or doxorubicin in NT8e cell lines, showed apoptosis by inhibiting Bcl-2 and increasing Bax, caspase-3, and poly-ADP ribose polymerase (PARP). However, these cells also exhibited cell cycle growth arrest at the G1/S phase, by down regulation of cyclins (D1, E2, B1, and A2), CDK2, and increased p21 levels. Down regulation of EGFR-ERK1/2 signalling molecules resulting in inhibition of cell proliferation. Thus in addition of curcumin with 5-FU/DOX can result in potentiation of chemotherapeutic effect [30].

The administration of curcumin at 100 mg/kg for 12 weeks in albino rat's carcinoma tongue induced by 4-nitroquinolone-1-oxide (4-NQO), showed that there was decreased expression of PCNA, Bcl-2, SOCS1 e -3, and STAT3. Curcumin also minimized the cellular atypia under microscopic analysis and diminished the expression of genes associated with EMT[31]. The hamsters bearing Buccal pouch cancer receiving 1% turmeric diet for 4 weeks showed decreased cell proliferation (diminished PCNA, cyclin D1, and Bcl-2) and PCNA labelling index, enhanced apoptosis (increased Bax, caspase-3, caspase-9, and cytochrome c, and decreased survivin) and apoptotic index, decreased inflammation (decreased Cox-2), and decreased MAPK activation (p-ERK and p-p38) [32].However, Curcumin significantly inhibited cancer cell migration and invasion in vitro and in vivo by modulation of MTOR's downstream target pS6 resulting in significant decrease of MMP-9[33].

With radiation dose of 4 Gy or greater radiation doses, curcumin showed increased radio sensitivity in vivo and vitro in SAS/luc cells. The enhanced radio sensitivity is seen through the inhibition of radiation-induced NF-κB activity and expression of effector proteins both in vitro and in vivo. In mice, the combination of curcumin with radiation showed better tumour control and no significant weight reduction [34]. Similarly synergistic effect was found with the dose of 5.50 and 6.75μM curcumin, along with 5 Gy of irradiation, resulting in the greatest reduction in cell migration capacity [35]. It also increased the radiation sensitivity of HPV negative in head and neck cancer cells through the inhibition of thioredoxinreductase in vitro and increasing survival in mouse model[36].In a similar study radiation along with curcumin showed inhibition of COX-2 expression and EGFR phosphorylation in vivo and in-vitro resulting in inhibited cell growth[37].

Curcumin when used as a freshly prepared mouth wash in Chemo-Radiotherapy treated patients significant reduction in severity of oral mucositis was noticed, compared to chlorohexidine mouthwash. Rapid wound healing and better patient compliance was added advantage in these patients [38]. Similar results were found when Curcumin was used with honey in oral mucositis [39].The reduction of oral microbial density and suppression of inflammation cascades may be the reason for the reduction in severity of the oral mucositis. Curcumin when used as multiple daily mouth washes it may prevent or decrease the severity of the radiotherapy induced oral mucositis.[40].

CONCLUSION

Curcumin is a naturally available drug which is not toxic even at high concentration. It can be used as chemo and radio sensitizer, in the management of OSCC patients to obtain optimum response at lower dose, thus reducing drug/radiation induced complications. Its use as chemo preventive drug in the management of potentially malignant disorders warrants further investigations and multicentre clinical trials. Even though its results are promising in oral cancer in vivo as well as in vitro, its efficacy in treatment OSCC patients' needs further evaluation.

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