



Alternative therapy in management of oral lesions- A review

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ABSTRACT

Potentially malignant disorders and oral cancer are majority of oral diseases effecting oral cavity. In spite of advances in treatment modalities, the survival rate of these patients has not been improved due to their adverse effects. To overcome these adverse effects alternative medicines such as turmeric, aloe vera, neem, green tea, photo dynamic therapy, CO₂ laser and stem cell culture etc are used. The aim of our review is to highlight on the applications of above mentioned alternative therapies in management of oral mucosal lesions.

Key words: Herbs, oral cavity, apoptosis, photodynamic therapy, stem cell, CO₂ laser.

INTRODUCTION

Alternative therapy is distinct from complementary medicine which is meant to accompany not to replace standard medical practice. It includes dietary supplement, mega dose vitamins, herbal preparation, special teas, massage therapy, magnet therapy and spiritual healing.

Herbs are composed of naturally occurring products like anthraquinone, phenols, glycosides flavanoids, carotenoids, alkaloids and nitrogen that help to regress the growth of oral lesions. These herbs act as anti-oxidant, antimicrobial, anti-inflammatory, antibacterial, antifungal, anti-proliferative and have anti-cancer properties. These herbal products are available in form of pills, syrups, tablets, oil, juice and ointment form. According to world health organization, medicinal plants would be the best source for obtaining a variety of drugs. [1]

Environmental factors such as areca nut chewing, smoking, alcohol intake infectious disease can lead to oral mucosal changes which act as key factor for inducing cancer.

These natural products act as antioxidant and help in modulation of genetic pathway. Hence using of these herbal products can help in treatment of premalignant lesions and decreases the risk of malignant transformation. The therapeutic role of plant in disease management is still in research due

to their less side effects and affordable properties. Other alternative therapies such as photodynamic therapy, stem cell therapy, CO₂ are also used in treatment of oral lesion.

CURCUMIN (TURMERIC)

It is yellow orange spice derived from family of *Curcuma longa* Linn belonging to the family Zingiberaceae. Curcumin is considered safe, non-toxic and effective alternative drugs because of its effects on various systems and therapeutic properties. The main ingredients in curcumin are curcuminoids, which has anti-inflammatory, anti-oxidant, anti-microbial, neuro-protective, cardio-protective, and anti-tumor actions. [2] It has a potent antitumor activity; it acts by increasing local levels of vitamin C and decreasing lipid peroxidation which cause DNA damage leading to apoptosis and inhibits cell growth of the malignant cells. It is also associated with inhibition of prostaglandin leukotriens and has fibrinolytic action and thus inhibits collagen synthesis. Curcumin has a beneficial role in the treatment of various precancerous conditions like oral submucous fibrosis, leukoplakia and oral lichen planus. It is available in form of powder and oil. [3] Cheng A, conducted prospective stage-I study on patient with oral leukoplakia and these patients were asked to take 500mg of curcumin/day for 5 months and found that there was significant reduction in burning sensation, and concluded that

curcumin can be used in chemoprevention of cancer. [4]

Sing V, et al conducted study on 10 patients of clinically and histologically diagnosed oral lichen planus. Turmeric ointment was given to apply topically 2 times a day for 3 months, significant improvement was observed in clinical symptoms. [5]

Curcumin holds a promising future in local therapeutic applications precise for oral diseases such as precancerous lesions and aphthous ulcers.

GREEN TEA

Tea is most commonly used beverage secondary to water, due to difference in their processing method they are divided into black tea, green tea and oolong tea. Green tea is produced by minimal oxidation immediately after harvesting and hence contains naturally occurring polyphenols. [6]

Green tea is derived from the plant *Camellia sinensis* and contains polyphenols, glycosides, leucoanthocyanins, and phenolic acid. Polyphenols present in green tea are Epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), epigallocatechin-3-gallate (EGCG), respectively. The polyphenols act as anti-inflammatory, anti-viral, and inhibit growth of cancer cells and prevent metastasis. It is available in form of dried leaves. [2]

Epigallocatechin-3-gallate is polyphenol, act as chemopreventive agent which binds to number of protein present in cell and activate mitogenic activates protein kinase (MAPK) and inhibit growth of cancer cell. Polyphenols induces apoptosis by activating p53 and its target p21 gene. [7]

Study showed promising results in patients with high risk of oral premalignant lesions, these patient received 3 doses of GTE (500, 750, 1000 mg/m²) vs placebo thrice a day for 12 weeks. This study showed a greater clinical response with the 750 and 1000 mg/m² GTE (58.5%) and 500 mg/m² (36.4%) vs the placebo arm (18.2%) suggesting a good dose-response effect of GTE in the oral premalignant lesions. [8]

Li et al conducted double blind study on 59 oral leukoplakic patient using mixed tea products (3g mixed tea capsule oral administration along with mixed tea ointment topical) for 6 month result showed that there was reduction in size of lesion in 37.9% of cases and 3.4% patient had increase in size of lesion. [9]

HONEY

Honey, is a natural product formed from nectar by honeybees. The biologically active constituents present in honey are flavonoids and phenolic compounds, vitamins, trace elements, amino acids and enzymes². The flavonoids and phenolic compound present in honey act as anti-oxidant, antibacterial, hepatoprotective, anti-inflammatory, hypoglycemic, antihypertensive, anti-proliferative and has anti cancer effects. [10]

Intralesional administration of honey inhibit role of tumor growth by inhibiting release of TNF, interleukin 1, 6, nitric oxide and polyADP ribose polymerase (PARP) activity and prevent DNA repair. Flavonoids present in honey induces apoptosis by activating mitochondrial pathway and releases cytochrome c protein which forms apoptosome complex leading to depolarization and inhibits cell proliferation. [11]

It has beneficial role in treatment of oral lichen planus, radiation induced mucositis and aphthous ulcer. [2]

Due to its beneficial roles it can be considered as potent and promising anticancer agent which require further research both in experimental and clinical studies. Sanatkhar. M et al conducted study on 50 patients of oral lichen planus with use of 20ml of cedar honey 3 times daily via swish and swallow technique along with standard treatment, and concluded that efficacy of topical honey was great with no adverse effect. [10]

In a study done by Hadad S.A. et al in 50 patients with different oral lesion, all group of patient were instructed to apply thin layer of pure honey using sterile cotton until there is complete resolution of lesion, after few days these patients reported with relief of pain within a week and resolution of ulceration and erythema in one month. [12]

ALOVERA

Also known as *Aloe barbadensis* Miller, *Aloe chinensis* Bak., *Aloe elongata* Murray, *Aloe indica* Royle, belongs to *allicaceae* family that grows in hot and dry climate¹⁰ it is also known as "first aid plant". [2]

The active components of aloe include anthraquinones, chromones, polysaccharides, and enzymes. These active components have anti-cancer, anti-tumor, anti-ulcer, and evacuating action and also increases proliferation of normal human dermal cells which help in healing of tissue. [13] Polysaccharides present in alovera inhibit

binding of benzopyrene to primary hepatocyte which prevent formation of potentially cancer initiating benzopyrene-DNA adducts leading to inhibition of tumor growth. [1]

It is used in treatment of oromucosal lesions such as oral submucosa fibrosis, oral leukoplakia, oral mucositis burning mouth syndrome and in aphthous ulcers. The Aloe vera gel play chief role in stimulation of the complement linked to polysaccharides, hydration, insulation and protection. It is available in juice, oil and ointment form. [2]

Auradha A et al (2017) conducted study on 14 patient of OSMF and were asked to take juice and apply 5mg of alovera gel 3 times daily for 3 month. Result showed significant reduction in burning sensation, increase in cheek flexibility and improvement in mouth opening. [14]

Reddy R et al (2017) conducted double blind randomized trial study on 40 patient of oral lichen planus and all the patients were asked to apply alovera gel 3 times daily for 2months. Result showed that there was reduction in pain scores and burning sensation after 18 week of therapy. [15]

NEEM [AZADIRACHTA INDICA]

Neem belongs to medicinal family and known as "the tree of 40 in Africa as it is considered in treatment of 40 different diseases. The main constituents of neem include nimbin, nimbidin, nimbolide, and quercetin and β -sitosterol were first polyphenolic flavonoids purified from fresh leaves of neem and were known to have antifungal and anti-bacterial, anti-arthritis, anti-pyretic and anti-tumor activity. [16]

The anti-microbial effect of neem is brought about by breaking down of cell wall in microbes and inhibiting the growth of microorganisms. It helps in management of cancer, by regulating cell signaling pathways and modulates the activity of various tumour suppressor genes like p53, pTEN), angiogenesis (VEGF), transcription factors, and induces apoptosis by acting on bcl2 gene. [17] Insoluble fraction like ethyl acetate and methanol ethyl acetate present in neem leaf inhibit tumorigenesis by modulating xenobiotic – metabolizing enzyme. It also induces apoptosis by activating NF-Kb signaling pathway. [18]

Subapriya conducted a study to evaluate the chemopreventive effect of ethanolic neem leave extract in 12 dye methyl benza anthracene(DNBN) induced hamster buccal pouch carcinogenesis and found that ethanolic neem leaves extract inhibit the

development of DNBA induced HBP tumors protecting against oxidative stress. [19]

Permal.E et al concluded in his study ethanolic neem leaf extract (ENLE) induces apoptosis by both extrinsic and intrinsic pathway and inhibit IGF signal and act as chemotherapeutic agents in cancer. [20]

TULSI [Occimum sanctum]

Tulsi is a small sub shrub and is useful herb with wide range of properties. It has been used in diabetic patients, as hepato protective and in cancer treatment. [21] It act as cox-2 inhibitor which avoid inflammation and decreases pain .The phytochemicals like dimethylbenzonic acid, ethyl benzene campher eugenol, lenolenic acid etc present in tulsi cause nuclear condensation, cell shrinkage, membrane blebbing and apoptotic body formation leading to apoptosis. It also inhibits multiplication and migration of cancer cells and induces apoptosis. [22]

Sreevastava.A.et el conducted study by using 1gram of tulsi paste and 1gram of turmeric in base of glycerine, and patients with osmf were asked to apply paste all over the mucosa 4-5 times a day for 15 min, the result showed significant reduction in symptoms of burning sensation and had significant improvement in mouth opening. [23]

PHOTODYNAMIC THERAPY (PDT)

PDT is a treatment modality that uses cytotoxic free radicals that are produced by administration of light sensitive drug, known as photosensitizer followed by light irradiation of an appropriate wavelength. It has been used in treatment of localized, extensive lesions and in treatment of cancer due to its specificity and sensitivity towards tumor cells. It causes tumor cell death directly or indirectly by damaging to tumor vasculature and by activating immune response against tumor. [24]

This therapy consist of 3 basic component ie photosensitizer (PS), visible light, and oxygen. The procedure is carried out by administration of photosensitizer intravenously, orally or by topical application. Then the light of specific wavelength is irradiated in to the target area which leads to activation of photosensitizer. [25] This activated photosensitizer produce ions which remove hydrogen from cell to produce free radicals. Further this free radical react with oxygen to produce highly reactive oxygen species which has cytotoxic effect on target cell leading to cell death. [26]

It is used in treatment of precancerous lesions such as oral leukoplakia and oral lichen planus. Maloth.K.N et al conducted clinical study on 13

patients of oral leukoplakia and 20 cases of oral lichen planus using ALA- photosensitizer(5-Aminolevulinic acid) and found 66.6% showed good response and 16.6% showed no response to PDT and concluded that PDT can be used as effective noninvasive treatment modality for precancerous lesions like oral leukoplakia and oral lichen planus. [27]

A clinical study conducted by Pretruksa et al on 44 patients of homogeneous leukoplakia by means of PDT using chlorin-e6 as photosensitizer, he found remission and reduction in size of lesion and concluded that PDT with chlorine-e6 can lead to considerable reduction of oral leukoplakic lesion and may be used in clinical practice. [28]

Recent Developments in PDT are Targeted PS Delivery, Nanotechnology in PDT, Vascular Targeted PDT, Two-Photon PDT, PDT-based Tumor-Vaccines Cancer immunotherapy. [23]

STEM CELL

Stem cell has self-renewal capacity with highly replicative potential. It is defined as immature or undifferentiated cells that are capable of generating daughter cells identical to themselves or of differentiating into diverse cellular phenotypes. There are 3 types of stem cell embryonic, germinal and somatic. Adult stem cell are commonly used which are derived from bone marrow. Cancer stem cell has no control over the cell numbers hence they are responsible for growth of tumor cells. Stem cells help in tissue regeneration and act as a delivery vehicle in the treatment of cancer. [29]

It induces neoangiogenesis by releasing cytokines and growth factors which result in formation of free radical scavengers and also stimulate formation of fibroblast which help in removal of altered collagen fibers and improves in cheek flexibility and help increase mouth opening in OSMF patients. [30]

Sankaranarayanan et al. did a clinical trial on a 43yrs old male patient suffering from OSMF for the past 10yrs. He took 40 ml of Bone Marrow, aspirated from posterior iliac crest, transported in Acid Citrate Dextrose and processed for mononuclear cells (MNC). The 4 mL of MNC concentrate containing 294 million was injected intra orally at various sites in the affected area under local anesthesia. Result showed gradually

relief from burning sensation, increased salivary secretion and increase in the mouth opening after injection. [31]

Vanikar et al. performed allogenic hematopoietic stem cell transplant (HSCT) with nonmyeloablative low-intensity conditioning in nine patients of Pemphigus vulgaris and found that there was regression of existing lesion within 24hours and at the end of 6 month new lesions stopped erupting. [32]

CO₂ LASERS

A widely used laser in dentistry as it does not penetrate deep into the tissue and has wavelength of 10600nm and is readily absorbed by water. It is used in treatment of precancerous lesions like oral leukoplakia, Lichen planus, and erythroplakia. [33]

Administration of CO₂ laser produces heat which result in contraction of collagen fibers, shrinkage of fibers to 1/3 of their length and vaporization of water from cell leading to protein degeneration and necrosis. [34]

Schoelch et al analysed on 70 patients with oral leukoplakia operated by using CO₂ laser and Nd-YAG laser, he found there was complete control of lesion in 29 cases and 19 cases had small recurrence by which he concluded that laser can be used as effective tool for surgery of oral leukoplakia. [35]

Yalcinkaya.E.S et al studied on 22 patient of oral leukoplakia who were treated with CO₂ laser with focus probe, result showed healing of lesions by secondary epithelization and areas appeared normal within 3 to 5 days. They Concluded that CO₂ lasers has effective role in management of oral leukoplakia. [36]

Conclusion

World health organization has identified more than 300 alternative therapies. Together with modern system of medicine alternative health science/therapies offer cheaper and easily adaptable solution to various ailments for positive health. As they have anti-inflammatory anti-fungal, anti-cancer, anti-microbial and anti-oxidant properties they have proven to be beneficial in treatment of oral mucosal lesions.

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