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The Potential of Natural Compounds for the Prevention and Treatment of Oral Cancer

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Abstract

Background: *Since ancient times, natural products, have been used for enhancing immune system dramatically. It is among the plants of intense commercial and scientific interest; hence, the aim of this study was to describe its chemistry and pharmacology aspect of natural compounds as a chemo preventive agent that advances attractive area of study.*

Methods: *PubMed, Cochrane Controlled Trials Register (CENTRAL) and Google Scholar were searched independently for relevant literature. The last search occurred in October 2020 . Other research material was obtained from Google. The following search terms were used, but not limited to: "natural product ", "bioactive compounds ", "medicinal plants, "anticancer ." Articles that were explaining the chemistry and pharmacology as an anticancer and chemo preventive agents were included.*

Results: *Eighty articles from PubMed, Cochrane and Google Scholar were eligible. Three webpages were included from Google. Results showed Despite the advances in the treatment of head and neck cancers, head and neck squamous cell carcinomas are still one of the fatal cancers worldwide. To that end, the development of chemo preventive agents for the treatment of oral cancer has attracted many researchers. Cancer chemo preventive compounds include natural or synthetic compounds that may prevent, arrest, or reverse the carcinogenesis at the premalignancy or early stage of the tumors.*

Conclusion: *Due to low toxicity, safety, antioxidant properties, high dietary acceptance high availability and affordability, fruits and natural compounds have been under investigation as treatment alternatives in recent years. This review paper assessed the anti-cancer properties of natural compounds such as tea, turmeric, neem, cranberry, and beta carotene. We investigated their active ingredients and mechanism of action and concluded that these natural compounds showed promising results for cancer prevention or as an adjunct treatment. More randomized clinical trial studies are needed to show definite results.*

Keywords: *Oral cancer, Natural products, Medicinal Plants, Bioactive compounds, Molecules, Phytochemicals, Curcumin, Anti-cancer.*

Introduction

Oral cancer is one of the dangerous and most common diseases worldwide, with severe complications when unattended [1,2]. Every year around 400,000 people worldwide are diagnosed with oral cancer and it is more common among men. Chemotherapy, surgery, and radiation therapy are popular treatments designed to inhibit the growth of oral cancer. Unfortunately, during these treatment procedures, many healthy cells in the body are also destroyed or damaged. To reduce oral cancer patients, early diagnosis and prompt treatment of potentially malignant diseases are essential. Thus, natural therapy and natural compounds can be suitable substitutes [2-4].

The isolation of phytochemicals from medicinal plants helps understand the therapeutic properties and pharmacology of the bioactive components [4-7].

These bioactive components interact with various transcription factors, protein kinases, and inflammatory mediators of the cancerous cells resulting in antimicrobial, antioxidant, anti-inflammatory, and anti-tumor behavior. For example, Curcumin is a yellow phenolic pigment extracted from turmeric. It is very well known for its anti-carcinogenic and therapeutic activities. Curcumin has anti-tumor activity in the oral cavity, which inhibits cell growth of the cancerous cells by inducing apoptosis in the cells. Gowda et al. in 2011 examined 12 patients with submucous fibrosis of the oral cavity and evaluated the clinical and pathological response to lycopene, i.e., carotenoid antioxidant. After lycopene treatment of 2000 mcg, twice a day for three months, improvement was observed without significant toxicity [1,4,7].

According to the statistics of Global Cancer Observatory (GLOBOCAN 2018), the total cases of cancer of the oropharynx, oral cavity, and larynx in 2018 was estimated at around 528,359. Oral squamous cell carcinoma (OSCC) is the most common head and neck cancer associated with the use of alcohol and tobacco and infection with oncogenic subtypes of the human papillomavirus. Treatment methods depend on the stage of the disease: Surgery is often recommended, followed by chemotherapy, radiation therapy, or both these methods [5,6].

Methods

This review adhered to the Preferred Reporting Items for all full text articles and related reviews selected from the electronic search were also performed . A detailed literature review was conducted to describe the chemistry, pharmacology, clinical properties and pharmacologic claims made as a chemoprevention by natural products.

Identification of articles

The literature search was done using PubMed, Cochrane Controlled Trials Register (CENTRAL) and Google Scholar. These databases were searched independently for relevant literature through October 2020. The search was re-run on May2021, and no new studies were found. Other research material was obtained from open searches using Google. The following MeSH (Medical Subject Headings) terms and keywords were used, but not limited to: "Natural Product" OR "Medicinal plants" OR "Curcumin" OR "Medicinal phytochemical".

Results

A total of Eighty studies from PubMed, Cochrane and Google Scholar were eligible. Results showed Despite the advances in the treatment of head and neck cancers, head and neck squamous cell carcinomas are still one of the fatal cancers worldwide. We investigated their active ingredients and mechanism of action and concluded that these natural compounds showed promising results for cancer prevention or as an adjunct treatment. More randomized clinical trial studies are needed to show definite results

Discussion

Cancer chemotherapy and the role of natural compounds

More than 60% of existing anti-cancer drugs are obtained in one way or another from natural sources [3]. Nature continues to be an abundant source of biologically active and diverse chemotypes. Although relatively few of the purely isolated natural products develop into clinically effective drugs on their own, these rare molecules often serve as models for more effective analogs and prodrugs. Chemical methodologies, such as manipulating biosynthetic pathways or complete or combinatorial (parallel) synthesis, are utilized for the synthesis. Also, improvements in the formulation may lead to more efficient drug delivery to the targeted sites in the patient's body. The conjugation of natural molecules to polymeric or monoclonal antibody carriers that specifically target epitopes to tumors of interest may lead to effective targeted therapies. The essential role of natural products in discovering and developing new oral anticancer agents has been studied. The importance of interdisciplinary collaboration for optimizing new molecular compounds from natural food sources is also extensively reviewed as an anti-cancer [4-8].

Treatment-related morbidity and mortality from Oral squamous cell carcinoma

(OSCC) remain a concern despite significant advances in immunotherapy, targeted therapy, surgery, and radiation therapy. Thus, there is potential for using natural compounds and molecules as anti-cancer drugs if their therapeutic potential is carefully analyzed.

The five-year survival rate for head and neck squamous cell carcinoma(HNSCC) patients has yet to improve significantly, despite advances in therapy, including surgery, radiation, and chemotherapy. Clinical trials, especially for the prevention of second primary cancer, have already confirmed the concept of chemoprophylaxis. Multiple aberrant or unregulated signaling pathways involved in the growth, survival, and apoptosis of head and neck squamous cell carcinoma (HNSCCs) cast doubt on the clinical efficacy of chemo preventive agents [1,3,5].

To evaluate the efficacy of these chemo preventive agents, there is an urgent need to identify new biomarkers that have predictive value for any clinical disease. Risk stratification can be used for a more specific approach to disease control. Natural agents appear to be promising molecular targets for chemoprophylaxis. Innovative development of chemo preventive treatment approaches based on appropriate patient selection is critical to meaningful impact [3,6].

Curcumin in Turmeric:

Cancer still is one of the most complex and leading diseases affecting the world's population. In developed countries, oral cancer is the third leading cause of death [9]. It is estimated that the number of new cases of all cancers worldwide will be 15.4 million in 2020 and more in 2021[10]. Oral cancer accounts for 2–4% of cancers diagnosed each year in the United States. It is a common neoplasm in the Pacific Islands in Asia and especially in India. Carcinomas of the oral mucosa are predominantly caused by fungal, chemical carcinogens, chemical stimuli, and although viral infection is also involved in the genesis of some oral neoplasms [11]. The development of neck and head squamous cell carcinoma (HNSCC) is closely associated with certain risk factors, such as alcohol and tobacco use.

Turmeric or Curcumin (diferuloylmethane) is a polyphenolic compound found mainly in South Asia. Previous pharmacological studies (in vivo) have shown that Curcumin exhibits analgesic, antioxidant, antiseptic, anti-inflammatory, anti-carcinogenic, chemotherapeutic, anti-infectious (against bacteria, virus, and fungi), chemo preventive, anti-cancer, and anti-platelet activity[12,13].

As a natural product, turmeric (Curcumin) is non-toxic and has various effects on various oral diseases[14-15]. About 40-85% of an oral dose of Curcumin passes through the gastrointestinal tract unchanged, with most of the absorbed flavonoids being metabolized in the intestinal and liver mucosa.

Curcumin is often added to bromelain formulations to enhance absorption and anti-inflammatory effects [13,16,17].

Thus, it holds a great promise as a therapeutic agent. In vivo trials of turmeric are widely conducted in individuals suffering from conditions such as pancreatic cancer, oral cancer, multiple myeloma, colon cancer, mastitis, diabetic nephropathy, myelodysplastic syndrome, psoriasis, peptic ulcer disease, precancerous lesions, periodontal disease, HNSCC, and more [18].

To convert Curcumin into a prophylactic or therapeutic agent, it is essential to consider the dose that produces the desired effect. Most cancer drugs have serious side effects and are highly expensive, so it is ideal to find an effective treatment without any side effects. The need of the hour is a drug with solid therapeutic potential and minimal side effects that can target multiple cellular and molecular pathways in cancer.

Derived from turmeric (Curcumin longa), Curcumin is one such agent. Since early times, it has been used as a healing agent for a variety of illnesses. Curcumin has anti-cancer properties and inhibits the proliferation of cancer cells in vitro and in Vivo. It induces apoptosis and inhibits angiogenesis. Over the years, it has been proved that Curcumin targets specific sites of cancer cells, thus regulating the survival or death of the cancer cells.

Preclinical studies of various oral cancer cells in model animals showed that Curcumin has anti-cancer activity in vitro. Compared to other effective anti-cancer medicines, Curcumin has anti-cancer effects at lower doses. The anti-cancer properties of Curcumin are due to its properties of inhibiting tumor initiation [10].

In India and Asian countries, turmeric has been used for over 2500 years. In 2009, Ayyalusamy Ramamurthis at the University of Michigan found that Curcumin in turmeric helps destroy cancerous cells by invading their cell membranes and interfering with their molecular pathways. The use of Curcumin makes the cells less susceptible to infections and even cancer. [15,16]

The anti-carcinogenic effect of Curcumin causes disturbances in the development of the cancerous cell cycle. The main features of the cell cycle development are DNA synthesis (S-phase) and the separation of two daughter cells (M-phase). Phase G2 is the time interval between phases S and M. This phase is essential; it allows cells to correct errors during DNA duplication, preventing the spread of these errors to daughter cells. Phase G1 is a period of commitment to developing the cell cycle, which separates phases M and S as the cells prepare for DNA duplication by mitogenic signals. Curcumin inhibits cell proliferation, induces apoptosis, and induces cell accumulation in the G2 / M phase of the cell cycle

(9, 12,14). Curcumin also affects intercellular adhesion proteins such as β-catenin and E-cadherin. It suppresses the production of cytokines associated with tumor growth by decreasing the expression of membrane surface molecules that play a role in cell adhesion through complex nonlinear pathways. Summary of mechanism action of curcumin is depicted in figure1.

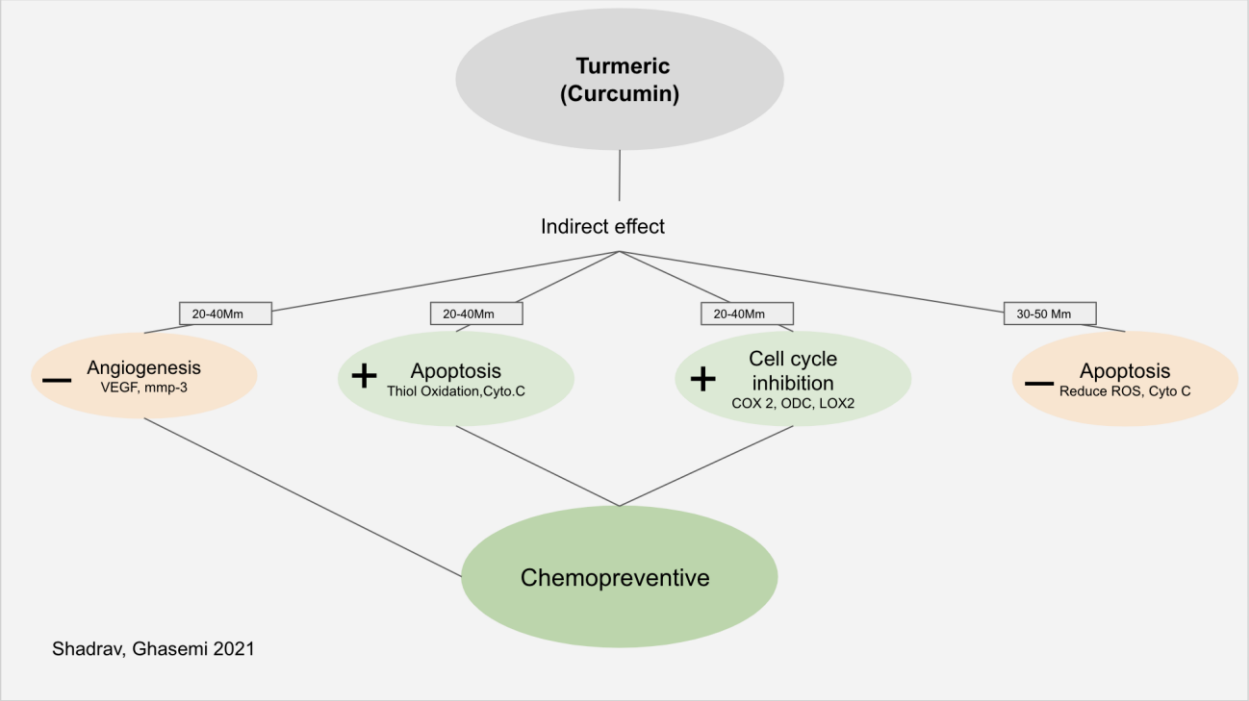

Figure 1. Mechanism of chemo preventive by natural curcumin in turmeric(the mechanism of curcumin to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor and preventing invasion and metastasis .curcumin modulates the activity of oncogenes, tumor suppressor genes ,several transcription factors and signaling pathways).

Turmeric saline (0.9%) is non-irritating and is believed to promote the healing and formation of granulation tissue. It is an economical and safe mouthwash. Saltwater mouthwashes are considered to be an excellent treatment for wounds in the mouth. The reason being saltwater or turmeric extract is not only a natural disinfectant but also relieves swelling from tissues. Mouthwashes containing medicinal properties such as turmeric or saline can be very economical and beneficial for the patient in terms of treatment and symptom relief. They effectively prevent complications in the follow-up and future use after completion of treatment procedures [13,14].

Recent developments in cancer treatments using the herb curcumin, a hydrogen donor, and a free radical scavenger that exhibits pro and antioxidant activity are studied. It binds metals, especially copper and iron, and can act as an iron chelator. [16].

Polyphenolic Compounds in Tea:

Tea has been known as one of the most popular drinks worldwide [17-18]. Tea is made from the leaves of the Camellia Sinensis plant and, depending on the manufacturing process, becomes black, red, green, or white tea. According to Mokhtar et al., 78% of the tea consumed worldwide is black tea, 20% is green tea, and 2% is white tea. Geographically, Western societies tend to consume back tea, while few countries in North Africa, alongside most Asian countries, drink green tea. White tea (oolong tea) is more confined in China and Taiwan [19]. There are multiple factors affecting tea compositions: climate, season, horticultural particles, and type and age of the plant [21]. According to several studies, the chemical structure of tea consists of minerals and compounds such as chromium, manganese, selenium, polyphenols, aluminum, fluoride, proteins, volatile organic compounds, and alkaloids (caffeine, theophylline) [17-18-20]. Comparing the different teas' compositions reveals that the green tea is more similar to the original tea leaves. According to NIH, polyphenolic compounds such as flavanols (also known as catechins) hold 30% of the dry weight of green tea leaves. The main catechins in green tea are (2)-epicatechin, (2)-epicatechin-3-gallate, (2)-epigallocatechin, and (2)-epigallocatechin-3-gallate (EGCG). In black teas, the major polyphenols are theaflavin and thearubigin (Table-1). [22,37]

Tea Type/Main Compound	Green	Black	White
Polyphenolic Compounds	The majority of catechin (flavonoids) includes: 1-Epigallocatechin-3-gallate (EGCG) 2-Epigallocatechin (EGC) 3-Epicatechin-3-gallate (ECG) 4-Epicatechin (EC)	Less catechin compared to Green tea and consists of more complex polyphenols: Thearubigins and theaflavins	Same amount of Epigallocatechin-3-gallate (EGCG) but less amount of the other catechins than green tea.

Table 1. Comparison between different tea types based on their composition

Multiple studies have shown that the polyphenolic compounds and gallic acids derivatives exhibit antioxidants and anti-cancer properties [18,23,24,25] (EGCG (the highest compound among the polyphenols) has received the most attention regarding anti-carcinogenic properties. [15]. Mechanism of action of polyphenols is summarized in figure 2.

Rahman et al. have studied the chemo preventive potential of natural compounds and demonstrated that EGCG inhibits cell growth, proliferation, and angiogenesis. [15]. EGCG arrests cell cycle at G0-C1 phase and down-regulates cyclin D1[26,27], and enhances cell apoptosis by P53 stabilization [28,29]. Moreover, it interrupts angiogenesis by inhibiting vascular endothelial growth factor (VEGF) production by tumor cells [30,31]. Therefore, it plays an inhibitory role in head and neck cancer development and progression. A study by Khafif demonstrated the role of EGCG in regulating the cell cycle in oral leukoplakia [29]. Schwartz performed a study on human oral cells and concluded drinking green tea (400-500 mg, 5 cups/day for 4 weeks) decreases the number of damaged cells in smokers by promoting cell apoptosis.[32]. D'Souza et al. stated that tea constituents and polyphenols might help prevent and control oral cancer [33-35].

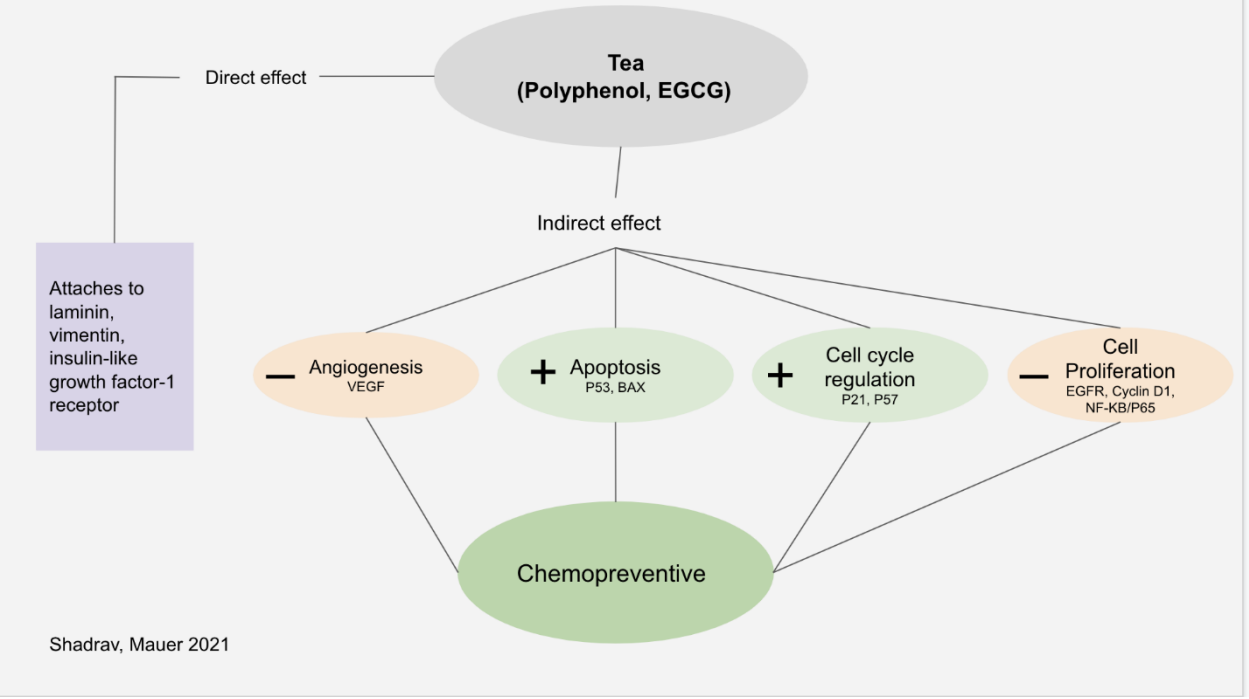

Figure 2 demonstrates some of the mechanisms that EGCG plays as a chemopreventive agent.

Although numerous studies have shown downregulation of cell cycles and angiogenesis by tea compounds, this effect is dose-related. [33-35] Consuming high doses of green tea extracts may cause hepatotoxicity [8,36,38]. A recent meta-analysis study by Fillipini indicated that due to several side effects related to high intakes of green tea and inconsistency in results require well-conducted and randomized control trials for further consolations of green tea on the risk of cancers. [39].

Azadirachta indica Neem:

Azadirachta indica also called "neem" is a typical large medicinal ageless tree known for its innumerate biological benefits and usually present in the tropical district. Being known to possess anti-inflammatory, immune-modulatory, and anti-carcinogenic properties, this plant became popularly known in the medical field. [40-42] Recent reveals that neem is an evident substance in preventing oral cancer [40]. Seed, leaf, and flower extracts of this plant can be implemented in diverse uses. [43-45] .Most interestingly extracts taken from the leaf containing glycoproteins, ethanols, and limonoids such as Nimbolide and Azadirachtin effectively fight oral neoplastic tissues [40].

Extensive investigations were done to demonstrate the chemo-protective character of this natural product. For this purpose, hamster buccal pouch carcinomas were used in most studies as carcinogenic models. The hamster carcinomas were used for their high resemblance to the oral squamous cell carcinoma present in the human body regarding its histology, gene expression, invasion tendency, and metastasis [42,46]. Inhibiting the expansion and growth of 7, 12-Dimethylbenz[a]anthracene (DMBA) in the hamster's buccal pouch was the first sign chemo-protective property of this substance. An overwhelming body of evidence indicates the importance of this component in oral cancer prevention due to several mechanisms explained below. Summary of mechanism of action of limonoids in neem is demonstrated in figure 3.

The first mechanism explains that this natural compound can prevent oral cancer through neoplastic cell proliferation impediment. Cancerous cells are generally known for their aptitude to reproduce in an unrestrained and unceasing manner. Consequently, the capability to avert cellular multiplication is a pillar for preventing neoplasms. Previous studies have shown advantageous effects of using neem extracts in hindering cancer cell proliferation [48,50]. In a study by Ricci et al., neem oil derived by methanolic extraction and defined as MEX was proven to have an antiproliferative ability. This is due to the cytotoxicity of MEX that is imputable to the radical structural changes of the plasma membrane, which includes the demolition of the membrane lipids and consequential loss of function [51]. Limonoids, terpenoids, and flavonoids found in ethanolic neem leaf extract are accountable for

monitoring DMBA-induced lipid peroxidation and elevating antioxidants [52,53] Gogate et al. confirmed the inhibitory effects of the neem on cancerous cell proliferation. His conclusion came after reporting a decrease in DNA damage and antioxidant induction formed by quercetin, a highly ethanol-soluble neem bioflavonoid [43,54,55].

The second important mechanism involves the role of the neem in modulating the xenobiotic-metabolizing enzymes. Xenobiotic metabolizing enzymes are significant chemopreventive components activated by neem components present in leaf extracts like limonoids. Their action is completed in two phases. The first phase is the inhibition of cancerous cell enzymes. This leads to the second phase, where carcinogenic cells' enzymes are detoxified. These two phases cause the prevention of cancer-causing-cells at an early stage, due to which neem is well known for its "double-edged" line of attack [44].

The third mechanism of neem's anti-cancer activity follows the prevention of tumor incursion and reducing angiogenesis. RECK protein is an essential protein responsible for regulating tumor markers involved in invasion and neo-angiogenesis. Alleviated expression of miR-21 and HIF-1α showed that nimbolide was an active agent in influencing Reck protein, leading to a significant decrease of invasion and angiogenesis mediators. [46]. Besides, it has been demonstrated that leaf extracts of neem can considerably lessen pro-cancer inflammatory cytokines and impede cell signaling and migration [49]. Besides, glycoproteins in the neem leaf enhanced the migration capability of monocytes and increased the cytotoxic effect of T lymphocytes. [45] Finally, neem can not only serve as a chemo preventive option but as a treatment strategy as well. It has been proved that an extract called "Super Critical CO2 Neem leaf Extract" or (SCNE) with its bioactive compound called NIM can modify cellular signaling in a direction that decreases several pro-tumor inflammatory mediators in oral squamous cell carcinoma [56]. Furthermore, neem extracts can lead to the death of cancerous cells through apoptosis and autophagy. [47] Investigations on DMBA-induced hamster buccal pouch oral carcinogenesis models have revealed that neem extracts help in the activation of a series of molecular reactions where there's an increase in the expression of caspase 8, caspase 3, Bim, Bax, Apaf-1, and PARP that are all involved in apoptotic cell death. This is also accompanied by continuous prevention of Bcl-2 expression [43,57,58].

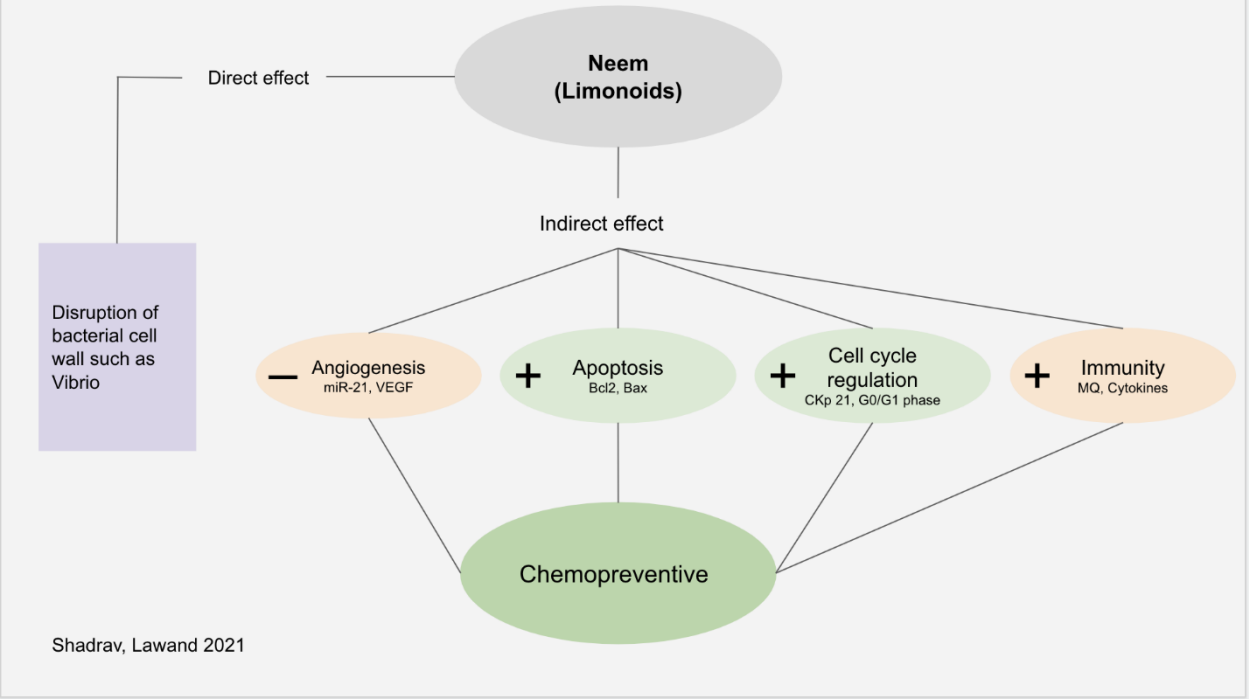

Figure 3. Mechanism of chemopreventive by natural limonoids in neem.

In brief, this natural compound shows a preventive potential in oral cancers and mainly oral squamous cell carcinoma. These facts promise its use as a regimen for preventing and treating oral cancers either alone or in combination with other compounds. Further research involving in vivo trials must be done to prove its preventive capacity in the clinical field.

Proanthocyanidins in Cranberry:

Cranberry -a fruit native to North America- has anti-adhesion mechanisms against microbial species in the oral cavity, stomach, small intestine, and colon [58-60]. There is a growing public interest in the research of oral cancer prevention and treatment with this fruit due to its diverse phytochemicals agents such as flavonoids, polyphenolics, carotenoids, dithiolitions, glucosinolates, indoles, isothiocyanates, protease inhibitors, plant sterols, allium compounds, limonene, selenium, vitamin C, vitamin E and dietary fiber [60,61]

There is a special polyphenolic compound known as Proanthocyanins (PACs) with chemo preventive and chemotherapeutic effects in many stages of oral carcinogenesis. This compound is abundantly found in fruits, nuts, chocolate, cacao beans, and berries. Studies show the cytotoxic effect of PACs against a wide range of cancers such as colon, breast, and prostate. It also has a selective inhibition

effect on oral cancer, especially oral squamous cell carcinoma (OSCC) proliferation [60,62,63]. Summary of mechanism of action of PACs is demonstrated in figure 4.

Chemo preventive characteristics of cranberries include induction of apoptosis in tumor cells [64], reduced ornithine decarboxylase activity [65], decreased expression of matrix metalloproteinase, anti-inflammatory activities, and modulating reactive oxygen species. [66]

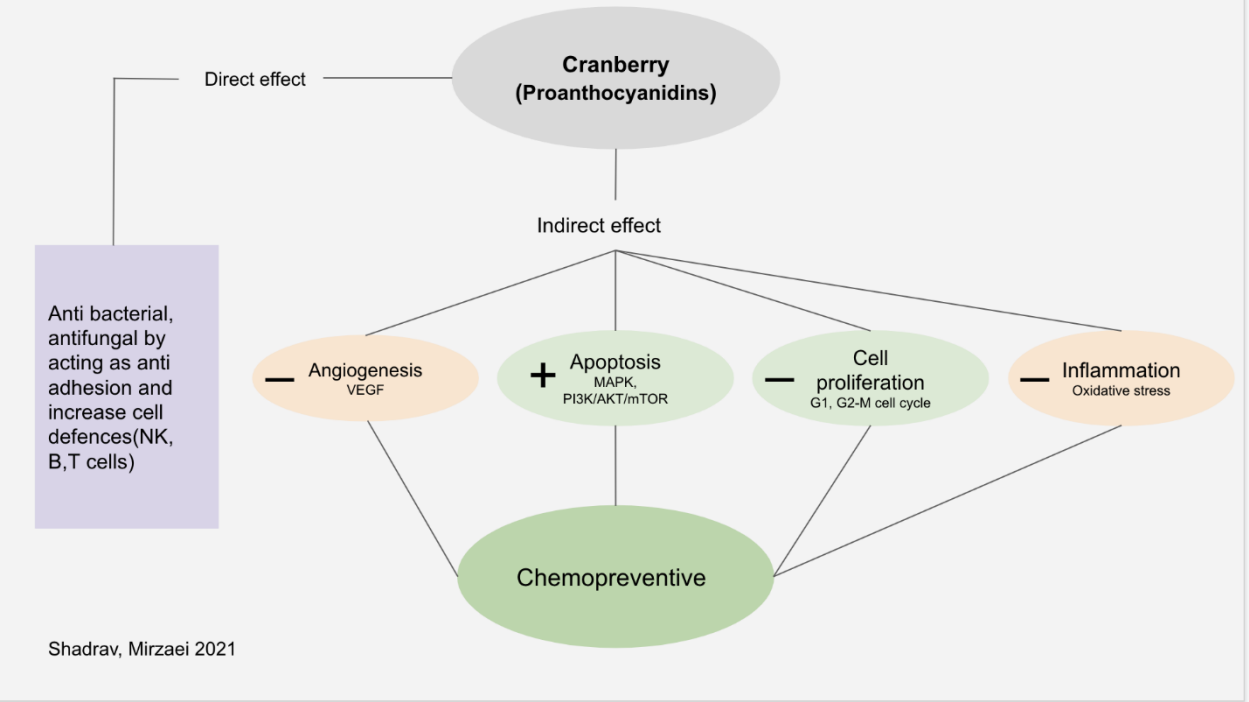

Figure 4. Mechanism of chemo preventive by natural proanthocyanins in cranberries

There are some review articles on berry-related anti-cancer mechanisms [67-69]. Weh et al. [67] reviewed the potential of cranberry and its derived constituents in cancer inhibition. They demonstrated 4 in vitro based studies revealing cranberry linked cancer inhibition in CAL27 by increasing apoptosis,[59] reducing cell adhesion [58], reducing cell density [70] via organic-soluble cranberry extract [59], reducing cell viability via total polyphenolic fraction HSC2 [71], increasing reduced glutathione levels via cranberry juice extract [72], reducing cell viability via organic-soluble cranberry extract [67,71], increasing apoptosis, reducing cell adhesion and reducing cell density via organic-soluble cranberry extract [59] in cell lines derived from the oral cavity. Further research, including clinical trials on human, animal models, and cell culture, needs to be done to elucidate the anti-cancer mechanism of berries.

The anti-carcinogenic activity of Beta carotene and Vitamin E:

Beta carotene is a pigment in plants that gives vegetables vibrant colors like red, orange, and yellow. Beta carotene is granted as a provitamin A Carotenoid, transforming into vitamin A (retinol). Also, beta carotene has a dynamic antioxidant role. Retinoids preserve the essential structure of vitamin A. Many derivatives of vitamin A have been produced to improve its therapeutic aspect. Carotenoids are compounds derived by 13-carotene, the predecessor for Vitamin A, and have antioxidant, anti-carcinogenic activities of their own [73,78]; Vitamin A plays a crucial role in the differentiation of normal epithelial tissues [72].

Vitamin E and Beta-Carotene together feature an excellent anti-cancer movement. Shaklar et al. designated that beta-carotene, vitamin E, and glutathione medicines decreased tumor burden. Moreover, beta-Carotene and glutathione gave more noteworthy levels of chemoprevention than vitamin E as single agents. [75] Garewal et al. state that beta-carotene has a considerable effect on oral premalignancy. Since it has no side effects, it is a great candidate for the prevention of oral cancer. [76] In hamsters, carotenoids stifled the carcinogenesis of actuated oral cancer and a cancer cell line by acting as a silencer that restrains the expressions of PCNA and cyclin D.[73-77]

Overwhelming alcohol consumers observed expanded anti-cancer effects of beta carotene towards the carcinogenic and genotoxic action due to cigarette smoking and alcohol ingestion. [79]. The mechanism of action of beta carotene and vitamin E is illustrated in figure 5.

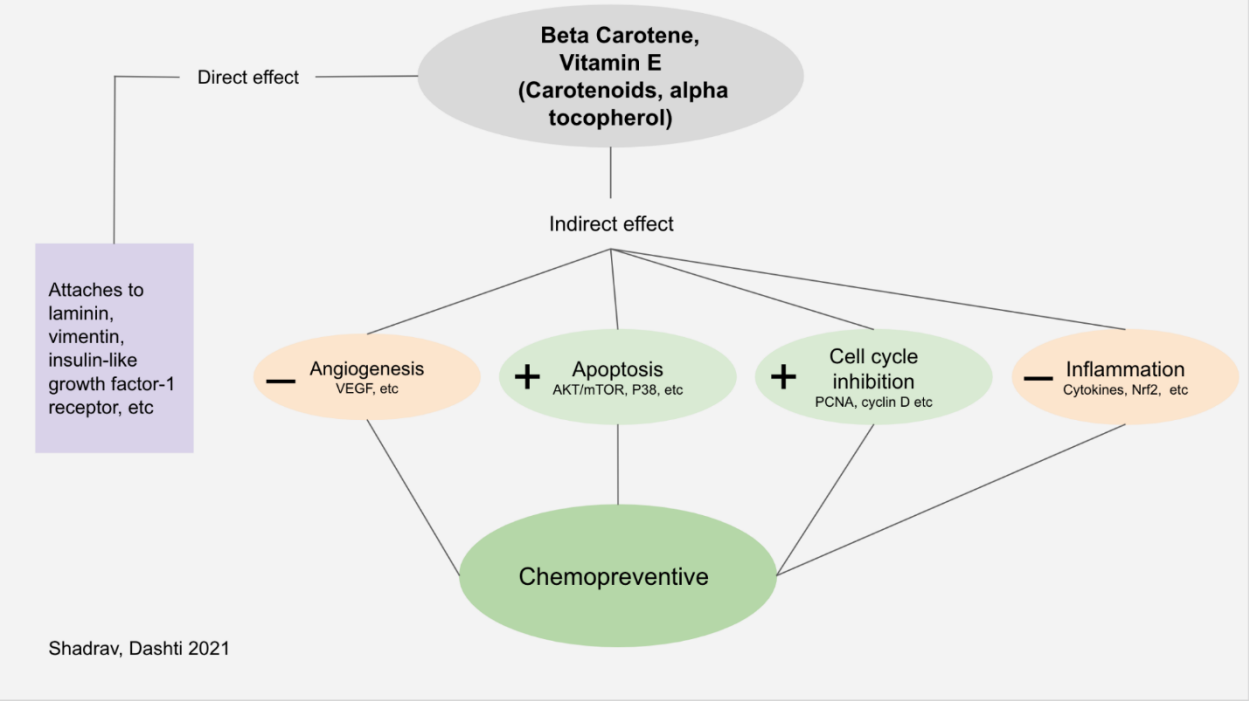

Figure 5. Mechanism of chemo preventive by natural carotenoids in Vitamin A and vitamin E.

There are a few disputes utilizing beta-carotene as a treatment of oral neoplasms, medications. Although vitamin A and beta carotene successfully recuperate oral manifestations, backslides and unfavorable impacts are common [80]. Nagao et al. state that beta-carotene and vitamin C were not much successful for clinical abatement and prevention against the advancement of cancer. Information from the Randomized Control Trials does not contribute to the theory that chemoprevention with this treatment is viable for oral leukoplakia [81].Table 2 illustrates natural compounds discussed above in order to demonstrate active ingredients and mechanism of action of each active ingredient for natural compounds, turmeric, tea, neem, cranberry, beta carotene and vitamin E.

Natural Compound	Active ingredient(s)	Mechanism of Action
Turmeric	Curcuminoids	Decreases tumor growth and cell adhesions Inhibits cell proliferation, Induces apoptosis Induces cell accumulation in the G2/M phase of the cell cycle
Tea	Polyphenolic compounds	Increases cell cycle regulations Increases apoptosis Decreases angiogenesis Decreases cell proliferation
Neem	Azadirachtin B, salannin and nimbin	Increase tumor suppressor gene(p53) Increase apoptosis (Bcl2) Decrease angiogenesis Decrease oncogene (c-Myc)
Cranberry	Proanthocyanidins (PACs)	Induction of apoptosis in tumor cells Reduce ornithine decarboxylase activity Decrease expression of matrix metalloproteinase and anti-inflammatory activities Induce G1 and G2-M cell cycle Decreases reactive oxygen
Beta Carotene	Carotenoid	Increase apoptosis Scavenger of lipophilic radicals

		Increase anti-inflammatory Oxidative agent for LDL
Vitamin E	Alpha tocopherol	May act as a ligand for not identified protein to regulate signal transduction and gene expression Decrease angiogenesis

Table 2. presents active ingredients and mechanisms of actions of the natural compounds.

Conclusion

Given the recent success of immunotherapy, nutritional immunology is also receiving more attention. Natural compounds and dietary components have been shown to affect immune cells and enhance the immune response to multiple conditions, including inflammatory diseases. For instance, berry, which contains multiple chemo preventive compounds, enhanced the function of natural killer cells and reduced neutrophil infiltration in an animal model and human patients due to the complexity of the tumor's microenvironment and immune system. Moreover, specific immune cells and their cytokines within the tumor have been regulated by natural compounds like beta carotene and Vitamin E and bioactive components of turmeric, tea, and neem. Still, a lot more research and studies can be done to dig into the reaction mechanisms involved in the natural compounds' anti-cancer activities, leading to the isolation of practical components and designing derivatives to treat oral cancer with minimal side effects.

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