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The Preventive and Therapeutic Roles of Natural Medicines in the Management of Oral Cancer

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Abstract. Cancer is a group of diverse disorders that have a genetic impairment and an uncontrolled proliferation of cells. Behavioural risk factors are closely associated with oral malignancies and expose oral fibroblasts to physical trauma and chemical irritation. The most common course of treatment of the late-stage case, surgical resection, has a high likelihood of causing facial deformities and problems with the key functions of the body. Traditional therapeutic methods, such as surgery, radiotherapy and chemotherapy have also been limited by adverse reactions, inability to be targeted, recurrence of the disease, and high cost of treatment. These obstacles have prompted research on more natural anticancer agents which have multi-targeted and selective action mechanisms. This review discusses the preventive and therapeutic usefulness of natural compounds in the management of oral cancer with reference to two important compounds; anethole and naringenin. Anethole is selective in exerting cytotoxic effect in oral cancer cells, suppresses cell migration through the inhibition of the epithelial-mesenchymal transition (EMT), and also regulates the expression of key molecular signaling cascades, including cyclin D1, p53/p21, ERK, NF- 3 kg B and Wnt. Naringenin, in its turn, enjoys anti-fibrotic effects in oral submucous fibrosis, a precancerous condition, in downregulating fibrosis-related markers (alpha-SMA, collagen I, TGF-b) and reinstating the normal shape of fibroblasts. Collectively, these compounds emphasize the opportunities of natural bioactive compounds to supplement traditional therapies, decrease toxicity, and offer new prospects of drug development. They require testing by further clinical research to confirm their effectiveness and safety.

Keywords: natural bioactive compounds, oral malignancies, anethole, naringenin, anticancer mechanisms

1. Introduction

Cancer is a diverse field of research that is based on the destruction of cellular genetic material (DNA). This injury interferes with the normal regulation of regular cells causing them to proliferate abnormally and abnormal cells develop that may invade the surrounding tissues and verify in other areas. Cancer being among the top death causes in the world is a major obstacle towards enhanced life expectancy in both developing and developed countries. According to 2020 statistics on cancer all over the globe, around 19.3 million people received a new cancer diagnosis, and the disease took around 10 million lives in the same year [1]. Cancer may develop in virtually any type of tissue or

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organs, in which case oral cancer actually pertains to cancerous growths in the mouth cavity or oral cavity, i.e. lips, tongue, cheeks, floor of the mouth, hard and soft palate, sinuses and pharynx. This kind of cancer is very common in the southeast of Asia especially in China. Advanced risk factors include tobacco smoking, excessive alcohol intake, and betel quid chewing; all those causes physical injury and chemical damage to the oral fibroblasts serving as initiators and stimulators toward oral carcinogenesis.

In recent clinical practice, although several methods exist in early detection of lesions on the mouth, many patients are still diagnosed when the disease has reached a higher stage. In these instances, they are normally managed by surgical resection of tumors [2]. The worst effects of surgery intervention are permanent disfigurement of the face as well as subsequent loss of functions in mastication, deglutition and phonation. Although standard treatment regimens are successful in managing the disease, they are often characterized by various negative side effects. The conventional therapeutic measures, which are surgery, radiotherapy, and chemotherapy, have side effects that are not desirable in the oral cancer treatment that include nausea, vomiting, diarrhea, alopecia, and increased risk of infection, as a result of immunosuppression. Traditional chemotherapeutic agents have other drawbacks and limitations such as non-specific toxicity, damaging normal and proliferating cells as well as cancer cells and pharmacologically and pathologically may not be optimal to proceed, resulting in disease recurrence even many years after supposed effective therapy, and may not be optimal. The latter clinical limitations and the high cost of the traditional cancer therapy have been a powerful force to stimulate scientists to look into the possibility of finding anti-cancer agents based on natural resources.

Cumulating evidence of knowledge demonstrates that a large part of the natural lies in providing therapeutic benefits over the conventional chemotherapeutic drugs mainly due to its potential to act using numerous, more discriminating pathways. In contrast to the conventional chemotherapy, which uses a non-selective cytotoxic mechanism that kills cells known to rapidly redivide, such as tubulin in cell division or DNA topoisomerases in DNA replication and repair are found in many bioactive molecules of natural origin. The others cause effects by exerting a finer control over cell fate, which could be cellular differentiation into the less malignant state, or programmed cell death. There are natural compounds that can avoid or reverse multidrug resistance in cancer cells, and these compounds may represent potential treatment methods in tumors due to the resistance to conventional therapy. Some natural anticancer agents also have the potential to alter the tumor microenvironment- for example by preventing angiogenesis or one or more immune responses locally and systemically-preventing tumor growth via indirect pathways which may be less toxic.

As an example, certain classes of compounds in traditional medicines like flavonoids in Traditional Chinese Medicine and an isolated constituent of plants like anethole have been scientifically confirmed as being active against oral cancerous cells. By taking advantage of selective cytotoxicity of these natural molecules in oral malignant cells, modern research has been keen to use such natural molecules as adjuvance to existing treatment regimens. Natural bioactive compounds are often found to have a synergist effect with conventional chemotherapy allowing clinicians to obtain the same or better therapy response with greatly reduced doses of chemotherapeutic agents- making direct reductions in dose-limiting toxicities in the patient. The systematic screening of natural molecules is a crucial approach to discovering more lead compounds that have anticancer proven activity, supporting the creation of the next generation anticancer molecules as well as introducing innovative supportive or adjuvant therapeutic methods. In addition to drug discovery, the study of natural medicines has a special value in the study of cancer biology and it can result in the identification of completely novel anticancer pathways. In the end, this study

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has enormous potential in alleviating the burden of cancer that hits the world health systems and societies in the future.

2. Natural compounds with anti-oral cancer activity

2.1. Anethole

Anethole (chemical name: 1-methoxy-4-[(E)-1-propenyl]benzene) is a natural organic compound extracted from plants such as fennel and anise. Numerous studies have confirmed its significant anti-oral cancer potential.

A specific study employed a variety of laboratory detection techniques to comprehensively evaluate the effects of anethole on multiple physiological processes, migration ability, and related signaling pathways of gingival carcinoma cells (Ca9-22 cell line), aiming to systematically assess its anticancer activity and clarify the underlying molecular mechanisms.

2.1.1. Selective cytotoxicity of anethole against oral cancer cells

Researchers used the LDH (Lactate Dehydrogenase) release assay—a common method for assessing cell membrane damage and cell death—to quantify the cytotoxic effect of anethole on Ca9-22 oral cancer cells.

The experimental design involved treating three cell types (Ca9-22 oral cancer cells, non-tumorigenic gingival epithelial cells [GEC], and gingival fibroblasts [GF]) with different concentrations of anethole and comparing their responses. Normal GEC and GF cells demonstrated strong tolerance to anethole, with median lethal concentrations (LC50) significantly exceeding 30μM. In sharp contrast, Ca9-22 cancer cells were highly sensitive even to low concentrations of anethole, with an LC50 of approximately 8μM [3]. This significant difference in sensitivity indicates that anethole exhibits low toxicity to normal oral cells while maintaining potent and selective cytotoxicity against oral cancer cells.

2.1.2. Inhibitory effect of anethole on oral cancer cell migration

The researchers further investigated the impact of anethole on the migratory capacity of Ca9-22 cells using the standard in vitro "wound-healing" (scratch) assay. After creating an artificial scratch in a monolayer of Ca9-22 cells, treatment with 3μM anethole significantly inhibited cell migration: only about 23% of the original scratch area was covered by migrating cells during the observation period. In contrast, cells in the untreated control group migrated freely, completely covering the scratch area (100%), indicating normal migratory behavior.

This experiment directly confirmed that anethole can effectively inhibit the migration of Ca9-22 oral cancer cells. The invasion and metastasis of Ca9-22 cells are closely associated with the epithelial-mesenchymal transition (EMT). EMT is a dynamic biological process in which epithelial cells lose their characteristic features (such as strong cell-cell adhesion and polarity) under specific physiological or pathological conditions and acquire mesenchymal cell properties (including enhanced motility and invasiveness). Pathological EMT is a key driver of cancer cell metastasis and tissue fibrosis, characterized by increased cell motility, loss of cell adhesion molecules, and downregulated expression of epithelial markers such as E-cadherin.

Western blot analysis (immunoblotting) in the same study showed that treatment with 10μM anethole promoted the expression of the epithelial marker E-cadherin and inhibited the expression of the key mesenchymal marker vimentin during EMT. These molecular-level results suggest that

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anethole inhibits the migration of oral cancer cells at least in part by blocking or reversing the EMT process.

2.1.3. Multi-pathway regulation of anethole in anti-oral cancer activity

The study also explored the specific molecular signaling pathways underlying anethole's anti-oral cancer effects, revealing its significant regulatory roles in multiple tumor-related pathways: First, anethole strongly inhibits the expression of cyclin D1, a protein critical for driving the cell cycle from the G1 to S phase. Second, it upregulates the expression of the tumor suppressor protein p53 and its downstream target p21—key regulators of cell cycle arrest and apoptosis. Furthermore, anethole significantly suppresses the activity of mitogen-activated protein kinase (MAPK) family members (including ERK1/2, p38, and Jnk), the pro-inflammatory and pro-survival transcription factor nuclear factor kappa B (NF-κB), and genes associated with the Wnt signaling pathway (often dysregulated in cancer). In summary, anethole effectively inhibits a network of oral cancer-related signaling cascades, leading to significant downregulation of cyclin D1 expression. This multi-targeted inhibitory effect demonstrates that anethole acts as a potent multi-pathway inhibitor, simultaneously suppressing several key drivers of cancer progression.

Collectively, anethole possesses a combination of anti-oral cancer properties: selective killing of cancer cells, inhibition of migration and metastasis, and multi-targeted regulation of pro-cancer signaling pathways. Experimental evidence strongly supports its potential as a promising natural compound for anti-oral cancer research and application.

2.2. Naringenin

2.2.1. Chemical structure of naringenin

In nature, naringenin primarily exists in its free aglycone form. Its related compound, naringin, is structurally a derivative of naringenin with a disaccharide unit (neohesperidose) linked to the hydroxyl group at the 7-position of the A ring via a β-glycosidic bond—i.e., naringin is the 7-O-glycoside of naringenin. The addition of this sugar moiety significantly increases naringin's molecular weight and water solubility (e.g., approximately 0.1% solubility at room temperature, rising to around 10% at 75°C) but also imparts a distinct bitter taste. The glycosyl group affects naringin's bioavailability, as it typically requires enzymatic hydrolysis in the intestine to release the active aglycone (naringenin) before systemic absorption can occur.

Naringenin is classified as a dihydroflavone with a flavanone core structure. Its A ring contains hydroxyl substitutions at the 5- and 7-positions (forming a 5,7-dihydroxy pattern), while the B ring has a hydroxyl group at the 4'-position. Together, these substitutions give naringenin its characteristic chemical structure: 4',5,7-trihydroxyflavanone.

2.2.2. Anti-fibrotic effect of naringenin

Oral Submucous Fibrosis Oral potentially malignant disorders (OPMDs) are a set of clinical conditions impacting the oral mucosa and have the risk to develop oral cancer. Oral submucous fibrosis (OSMF) is, however, one of them and is a rather insidious, chronic, and progressive disease that cannot be reversed to a great extent. It is marked by progressive pathos of fibrosis (scarring), increased collagen deposition of submucosal tissue and subsequent atrophy of superimposing epithelial zone [4]. Some etiological factors of OSMF; including betel quid chewing are shared with

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oral squamous cell carcinoma (OSCC), but there is no clear understanding of the specific molecular processes leading to malignant transformation of fibrosis to cancer.

The experimental study has reported evidence of anti-fibrotic property of naringenin in OSMF [5]. Researchers had created an in vitro oral fibrosis model in this study by exposing human gingival fibroblasts (HGFs) to arecoline a major causative agent of OSMF, which is the primary alkaloid occurring in betel nut. They then compared the group with the model of fibrosis which was treated with arecoline and naringenin to determine how naringenin inhibits the effect of arecoline on fibrotic degeneration. The anti-fibrotic activity of naringenin was evaluated based on cell morphology observations as well as the examination of the major fibrosis markers. Acoline-treating fibroblasts alone exhibited clear morphological aberrations (a rise in cell density, disorganized and a substantial loss of the typical elongated and spindle-shaped morphology), which is suggestive of an arecoline-induced fibrotic morphology. Relatively, co-treated cells of arecoline and naringenin, however, developed some evidence of normal fibroblast morphology, reduced myofibroblast density (activated, contractile fibroblasts central to fibrosis), recovered spindle-like morphology, and was organized. This indicates that naringenin is able to reverse arecoline induced morphogenesis to some extent thereby proving its anti-fibrotic property. Regarding molecular markers, the α-Smooth Muscle Actin (actin 067 31 49), Collagen Type I (Col-type1, the primary collagen deposited in fibrosis), and Transforming Growth Factor-beta (TGF-067) levels were significantly greater in the group where the only treatment was arecoline in relation to the untreated control [6]. Significantly, cells of HGF that were co-treated by naringenin and arecoline exhibited significantly reduced expression of these markers as compared to the control group of arecoline. In particular, co-treatment with naringenin had a substantial suppressive effect on α-SMA (which reflects the suppressed activation of myofibroblasts) and Col-type1 (which reflects a reduced synthesis of collagen), and also had a powerful inhibitory effect on TGF-β-expression, which shows that naringenin suppresses the pro-fibrotic signaling cascade triggered by arecoline [7].

Overall, the preliminary evidence collected in the course of exploratory studies suggests that naringenin has the potential of anti-fibrotic effect in the alleviation of arecoline-induced fibrosis in human gingivial fibroblasts. This potential is evident in two major aspects, first, naringenin inhibits the excessive deposition of extra cellular matrix (ECM) proteins like collagen by regulating fibrosis-related cellular pathways; second, naringenin recovers normal fibroblast morphology, cell viability, and counters the cytotoxic activities of arecoline. Naringenin inhibits pathological collagen deposition and induces the re-establishment of normal cellular architecture in a manner that indicates the clear anti-fibrotic effect by down-regulating essential fibrosis markers (receptors of TGF- beta and PI3K- Akt) and by controlling the key signaling pathways.

3. Conclusion

Being a malignancy and having strong dependency on certain factors in our lifestyle, oral cancer remains a serious problem in clinical management. Among these difficulties there are the insufficient specificity of conventional treatment methods, serious toxic side effects, morbidity of organ functions and recurrence of disease in the long run an acute need has been identified in more effective, specific, and low-toxicity treatment methods. The structural diversity and multi-mechanistic approaches of action provided by natural bioactive molecules is a potential answer to this unmet requirement. The two natural compounds covered in this paper, anethole and naringenin, are no exception and each of them has anti-oral cancer effects at different and complementary stages.

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The study on anethole has demonstrated that anethole can selectively cause death to the existing oral cancer cells and cause minimal death to the normal gingival cells- directly relating to the fundamental flaw of conventional chemotherapy (no differentiation between cancer cells and healthy cells). Notably, the anti-tumor effect of anethole cannot be explained by a single pathway: by suppressing the movement and invasion of cancer cells, disrupting the process of EMT; by restoring normal cell division, upregulating the tumor-repressive p53/p21 pathway; and by all means at the same time stabilizing the activity of critical pathways of pro-cancer signals (such as ERK, NF--B and Wnt). This is a multi-dimensional, synergistic intervention that allows anethole to fight the development and progression of tumor more thoroughly. Conversely, studies conducted on naringenin are centered on oral carcinogenesis preventive or interceptive phase- that is, of oral submucous fibrosis (OSMF) which is a well-known precancerous state. It is experimentally established that the naringenin is able to reverse the fibrotic transformation of fibroblasts, which is caused by arecoline (arecoline is the major carcinogen of betel quid). It does so through suppressing the expression of key fibrosis markers (alpha-SMA and Collagen Type I) and by regulating central pro-fibrotic receptors (TGF-B) that cause abnormal ECM deposition and normal cellular morphology. This underscores the high relevance of naringenin and its analogues in the possible prevention of the malignant progression of oral precancer lesions, which is a vital preventive measure. Finally, natural bioactive molecules, examples being anethole and naringenin can be utilized at two important points in the oral cancer continuum: specifically destroying the pre-existing cancer cells and at the stage of the formation of precancerous conditions. Not only are they highly promising when used in conjunction with conventional drugs to help increase the efficacy and lower the toxicities, but they also serve as invaluable lead compounds in exploring the discovery of new anticancer pathways and gaining future generations of targeted therapy.

Although a majority of the available evidence is based on preclinical experiments that need extensive studies into the in vivo activity, comprehensive toxicology and clinical translation, it is not doubted that the more thorough the research into natural medicines, the greater their implication. This is required in the creation of safer and more effective measures of preventing and treating oral cancer, which will eventually help reduce the worldwide cancer burden.

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