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REVIEW ARTICLE

Chemoprevention of natural product against oral cancer: A comprehensive review

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Abstract

Introduction: Oral cancer is considered the sixth most common form of cancer worldwide. It causes significant morbidity and mortality, especially in low socioeconomic status groups. However, Cancer chemoprevention encompasses the use of specific compounds to suppress the growth of tumours or inhibit carcinogenesis. Natural products have been identified as one of the most significant sources of anti-cancer agents. Meanwhile, several synthetic drugs exhibit potential cytotoxicity and can induce a wide range of degenerative diseases. *Aim of the review:* This review aims to determine the various plants, vegetables, and fruits possessing natural chemotherapeutic agents against oral cancer cells. *Materials and methods:* A comprehensive review of findings reported in articles retrieved from searches of computerised databases, hand searches, and authoritative texts. Inclusion databases include PubMed, Medline, Web of Science, Scopus, and Scientific. Exclusion Computerised databases*:* Wikipedia or unknown sources. *Results:* Natural products have fewer side effects, high selectivity, low toxicity, and eliminate cancer cells. Thus, the application of natural products as alternative oral and other cancer therapies has recently demonstrated remarkable progress. *Conclusion:* Natural products have been widely used in developing oral anti-cancer drugs. Most of these natural products present bioactive chemical agents and novel mechanisms of action, such as the inhibition of tumour cell growth, the induction of apoptosis, DNA damage, and the inhibition of topoisomerases I and II. In future, the successful integration of natural products in oral cancer chemoprevention field depends on the advancement of molecular targeting, personalised approaches, and the exploration of novel drug delivery systems. Furthermore, integration of preclinical findings in clinical trials will be important for translating research into impactful interventions.

Keywords: cancer chemoprevention; natural products; plants; vegetables; fruits; oral cancer, head and neck cancer.

INTRODUCTION

Natural products produce several highly diverse secondary metabolites optimised for biological functions.[1] In order to improve the specificity and cover a very wide range of functions, natural products have been naturally selected for centuries depending on the origin, habitat, and the specific activity performed in the organism of origin. These intrinsic features have increased the use of natural products as healing agents and continue to be the most important source of potential therapeutic preparations.[2] A wide variety of these products are expected to complement conventional pharmaceuticals in treating, preventing, and diagnosing diseases.[3]

Natural products play diverse roles in humans and cover a wide range of disease targets, such as diabetes, inflammation, cancer, neurological

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diseases, cardiovascular diseases, liver damage, bacterial, fungal, and malarial infections.[4] A heat-processed onion extract was able to suppress carbohydrate absorption through the inhibition of intestinal sucrose by Amadori rearrangement compounds, thus reducing the postprandial increase of blood glucose in diabetic patients.[5] For neurological diseases, the cannabigerol obtained from Cannabis sativa has anti-inflammatory and anti-oxidant effects on NSC-34 motor neurons as demonstrated by a reduction in the Interleukin 1 Beta (IL-1β), Tumour Necrosis Factor Alpha (TNF-α), Interferon Gamma (IFN-γ), and Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) protein levels.[6] Meanwhile, the use of polar extract and chemical ingredients such as astragaloside IV of Astragalus membranaceus root has been reported in cases of cardiovascular diseases.[7] The product is often employed as a tonic herbal drug and exhibited a protective effect on cardiomyocytes exposed to oxidative stress through an increase in the respiratory capacity and mitochondrial Adenosine Triphosphate (ATP) production. Fucoidan, a sulphated polysaccharide found in seaweeds, was able to protect against hepatotoxicity induced by acetaminophen in a mouse model.[8] The researchers suggested a plausible mechanism related to nuclear factor erythroid 2-Related Factor 2 (Nrf2)-mediated oxidative stress in liver diseases. In cancer studies, flavonoids isolated from *Glycyrrhiza uralensis* (Chinese liquorice) could induce differentiation of melanoma B16-F10 cells or promote apoptosis.[9]

Several naturally-occurring compounds from vegetables and herbs exert chemo-preventive properties against carcinogenesis. Diets rich in vegetables, fruits, and legumes contain significant amounts of antioxidants that are protective against the deleterious action of free radicals.[10] Substances found in natural products have cytotoxic properties with several different mechanisms of action, such as tumour cell growth inhibition, apoptosis induction, Deoxyribonucleic Acid (DNA) damage, and topoisomerases I and II inhibition. Furthermore, the combination of plant-derived compounds in combination with anti-cancer drugs demonstrated great potential in destroying tumour cells and non-toxic to normal cells, such as lymphocytes and fibroblasts.[11]

Numerous studies have reported the potential inhibitory effects of phenolic compounds on cancer invasion and metastasis.[12] Natural plant metabolites are divided into blocking and suppressing agents. The former inhibits the tumour initiation step by preventing carcinogen activation, whereas suppressing agents inhibit tumour cell proliferation during the promotion and metastasis phases of tumorigenesis.[13] Natural products could provide diverse lead structures, which will be employed as templates for the construction of novel compounds with enhanced biological properties for the chemoprevention of cancer cells. Selective analogues produced by the combination of natural product templates and chemistry have a higher chance of success.[14] This review aims to provide a comprehensive revision on natural products with chemopreventive potential against oral cancer, emphasising their mechanisms of action and therapeutic implications. By exploring the role of natural compounds in controlling oral cancer, this review aims to contribute to the development of effective strategies for cancer prevention and management. Through highlighting the promising avenues for utilising natural products in oral cancer control, this review seeks to underscore the significance of integrating natural compounds into conventional therapeutic approaches for improved patient outcomes.

Oral Cancer

Oral cancer includes cancer of the lip and oral cavities, such as buccal mucosa, gingiva, hard palate, tongue, and floor of the mouth. It is considered the sixth most common form of cancer worldwide.[15] Oral cancer causes significant morbidity and mortality, especially in low socioeconomic status groups.[16] Less than 50% of oral cancer patients survive for five years after metastasis. This low survival rate has been attributed to delayed diagnosis and inappropriate therapy.[17] Overall, people with low socioeconomic status and lower educational qualifications display higher incidence and mortality, lower quality of life, and survival rates due to restricted access to treatment and social support.[18] Oral cancer is multifactorial and the common risk factors include smoking and concurrent smoking, alcohol consumption, betel quid chewing, and viral infections, such as Epstein–Barr virus and human papillomavirus (HPV).[19] These risk factors lead to genetic variations in tumour suppressor genes Adenomatous Polyposis Coli (APC, p53), proto-oncogenes (Myc), oncogenes (Ras), and genes controlling normal cellular processes, such as Eukaryotic Translation Initiation Factor

3 Subunit Eand Glutathione S-Transferase Mu 1(EIF3E, GSTM1). The potential to induce oral cancer was associated with defects in processes, such as segregation of chromosomes, genomic copy number, loss of heterozygosity, telomere stabilities, regulations of cell cycle checkpoints, DNA damage repairs, and Notch signalling pathways.[20]

Cigarette smoke contains more than 60 cancer-promoting elements, which can be essentially separated into three distinct groups: nitrosamines, benzopyrenes, and aromatic amines.[21,22] These chemicals are known as pre-carcinogens given that they must undergo coordinated alterations by oxidative enzymes for the final product to have a low number of electrons. Resultantly, the chemicals become a covalently binding agent to the DNA and generate an adduct mutated region.[23] In a previous study, alcohol reportedly increased the permeability of oral mucosa, dissolved lipids components of the epithelium, caused epithelial atrophy, and interfered with DNA synthesis and repair.[24] Genotoxicity and mutagenic effects were also reported, thereby causing decreased salivary flow, affecting the liver's ability to metabolise toxic or potentially carcinogenic compounds and chronic intake which was associated with impairment of innate and acquired immunity.[25] The human papillomavirus (HPV) is a group of host-specific DNA viruses with significant epithelial cell specificity and possesses morphological resemblance between oropharyngeal and genital epithelia. The virus is equipped with oncogenic potential due to its ability to insert specific DNA fragments into the host cellular genome. This integration facilitates the elimination of certain essential functions of tumour suppressor factors, thereby resulting in defects in apoptosis, DNA repair mechanisms, cell cycle regulation, and cell immortalisation.[26]

The subtypes and various sites of oral cancer differ in aetiology epidemiology and survival rate.[27] Oral squamous cell carcinoma (OSCC) arising from the oral epithelium accounts for approximately 90% of all oral cancers. Meanwhile, the remaining 10% comprises malignant intraoral salivary gland tumours, lymphoma, melanomas, leucoplakia, erythroplakia, and several benign oral cavity tumours.[28] No pain is experienced during the initial stage of OSCC but a burning sensation or pain may develop in the advanced stages.

The common developing sites of OSCC are the lips, tongue, and floor of the mouth.[29] Oral squamous cell carcinoma (OSCC) may resemble erythroplakia or leukoplakia, any of which may eventually develop into a necrotic-looking ulcer with irregular, raised indurated borders, or into a broad-based exophytic mass.[30] Given that leukoplakia and erythroplakia will eventually transit into malignant cancers, they are traditionally referred to as two oral mucosa precancerous lesions. Leukoplakia is a visible white area while erythroplakia is characterised by a red area that may be flat or slightly raised and frequently bleeds when scraped.[31] It is difficult to predict the behaviour of any of the lesions. Nevertheless, the survival rate of oral cancer patients is increased if the disease is detected at an early stage.[32] Salivary gland cancers could originate in either the major or minor salivary glands. Approximately 80%, 15%, and 5% of these tumours arise in the parotid gland, submandibular gland, and the minor and sublingual salivary glands respectively.[33] Mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), non-specified adenocarcinoma, and salivary duct carcinoma are the most common histopathologic types of OSCC.[34]

Carcinogenesis is a complex process that occurs at the phenotype and genotype levels. Cancer development is driven by the accumulation of genetic and epigenetic alterations disrupting the homeostatic equilibrium between cell proliferation and cell death.[35] Oral carcinogenesis is characterised by three distinct phases: initiation, promotion, and progression.[36] A premalignancy stage occurs in the transformation of normal tissue into a malignant one.[37] The development of oral cancer is a multi-stage process that progresses sequentially from hyperplasia to dysplasia to carcinomas. Nonetheless, the disease is already at an advanced stage in patients at the time of diagnosis in most cases. Oral cancer is highly aggressive evidenced by its migration and invasion of distant organs.[38]

Oral carcinogenesis mechanisms need to be elucidated to improve the survival curves that have plateaued over the past two decades and have remained among the worst of all cancer types.[39] Multiple genetic events alter the normal functions of oncogenes and tumour suppressor genes, thereby leading to increased production of growth factors or numbers of cell surface receptors, enhanced intracellular messenger signalling, and increased production of transcription factors.[40] The combination of these

events and the loss of tumour suppressor activity culminates in cell phenotype with increased proliferation rates, loss of cell cohesion, and the ability to infiltrate local tissue and spread to distant sites.[41] Tumour suppressor genes could be inactivated through genetic events, such as mutation, loss of heterozygosity, or deletion, or by epigenetic modifications including DNA methylation or chromatin remodelling.[42] Over-expression due to gene amplification, increased transcription, or structural alterations due to mutations leading to increased transforming activity are possible oncogene activation pathways.[43] Overall, tumorigenesis requires multiple essential elements, such as limitless replicative potential, self-sufficient growth signals, lack of anti-growth signal sensitivity, the ability to evade apoptosis, and increased angiogenesis, invasion, and metastasis.[23]

The current treatment options for oral cancer include surgery, radiation, chemotherapy, and targeted drug therapy. Hence, a multi-disciplinary approach in which coordinated efforts of dental practitioners, chemotherapy oncologists, surgeons, nutritionists, and radiation oncologists come into action.[44] Numerous factors are considered and the treatment is tailored individually to the patient's needs, quality of life, and survival rate.[45,46] recommended that the risk of treatment-related complications should be evaluated based on physiological age, comorbid conditions, such as cardiopulmonary status, a lifestyle involving smoking or alcohol consumption, surgical resect ability, and patient expectations.

Surgery has been the main option for the treatment of head, neck, and oral cancers. Nevertheless, the choice of surgical treatment depends on tumour location, size, proximity to bone, and depth of infiltration.[47] Surgery can broadly be divided into resection and reconstructive components. Resective surgery includes the removal of the primary tumour, managing the cervical nodes, and establishing a tracheostomy surgical airway if required. Reconstructive surgery essentially involves minimising the morbidity of the surgery, such as the replacement of tissue, and the effects on speech, swallowing, and mastication.[48] Radiotherapy involves the use of ionising radiation in which energy is transferred to destroy cells in a targeted area by altering cellular DNA, preventing growth, and multiplication.[49] Additionally, chemotherapy could be offered for curative purposes in combination with radiotherapy or alone for palliative purposes.[50] Chemotherapy utilises certain chemicals to kill cancer cells by inhibiting the synthesis of DNA strands, which stops cellular proliferation.[51] Unlike other approaches that are only able to treat cancers in confined areas, chemotherapy can be used to treat metastatic cancer. Nitrosoureas, antimetabolites, antibiotics, alkylating agents, steroid hormones, and plant alkaloids are the main categories of drugs used in chemotherapy.[52]

Despite the increasing effectiveness of cancer treatment, the treatment choices are associated with short- and long-term side effects.[53] Surgical complications include functional limitations on speech, mastication and swallowing, damage to the cranial nerves and the associated neurological disorders, chronic fistulas, and healing issues aesthetically, such as severe disfigurement and prosthetic rehabilitation.[54] Trismus may develop in either maxillary surgery involving the origin of medial and lateral pterygoid muscles, or mandibulectomy encompassing any of the masticating muscles.[55] Oral complications of chemotherapy include pain, infection, haemorrhage, xerostomia, as well as neurological and nutritional problems.[56]

Oral mucositis is an iatrogenic condition of erythematous inflammatory changes that may occur in patients receiving chemotherapy. The severity varies from localised to generalised erythema, frank ulceration, and haemorrhage.[57] Postoperative complications, such as xerostomia, dysgeusia, osteoradionecrosis, soft tissue necrosis, and spinal cord myelitis may occur in patients undergoing radiotherapy.[58] The oral morbidities of radiotherapy include, but are not limited to increased susceptibility to dental caries and periodontal disease.[59] Oral disorders may affect systemic health due to altered or reduced intake of nutrients, calories, vitamins, and minerals. These events may have systemic effects on energy levels such as fatigue, mood (depression), and cardiovascular health.[47]

Oral cancer arises from a complex interplay of molecular alterations that disrupt normal cellular processes and regulatory mechanisms. At the genetic level, mutations in tumour suppressor genes, such as *p53*, *adenomatous polyposis coli* (APC), and oncogenes, such as *Ras* and *Myc*, lead to dysregulation of cell cycle control, apoptosis, and DNA repair pathways, thereby promoting uncontrolled cell proliferation and tumour growth. Epigenetic modifications, such as DNA methylation and histone modifications, further contribute to the silencing of tumour

suppressor genes and activation of oncogenes by altering chromatin structure and gene expression profiles.[60] Dysfunctional signalling pathways, including the PI3K/Akt/mTOR pathway, MAPK pathway, and Wnt/β-catenin pathway, drive oral cancer progression by promoting cell survival, proliferation, angiogenesis, and metastasis. Moreover, interactions between cancer cells and the tumour microenvironment, characterised by inflammation, angiogenesis, and immune evasion mechanisms, play a critical role in tumour growth and invasion. Additionally, viral infections, particularly HPV, contribute to oral carcinogenesis through the integration of viral DNA into the host genome, disrupting cell cycle control and tumour suppressor pathways.[61]

Natural Products against Oral Cancer

Primary chemoprevention refers to reducing the risk of cancer development. Secondary chemoprevention involves reducing the risk of existing cancer from progressing.[62] Tertiary chemoprevention is defined as the administration of agents to prevent the recurrence of primary cancer that has been completely treated.[63] Meanwhile, cancer chemoprevention involves the use of both natural and synthetic compounds. Natural compounds appear either in a crude form or as chemically defined extracts.[64] The concept of using naturally derived chemicals as potential chemopreventive agents has significantly advanced the field. Recently, the focus has been directed toward molecular targeting of chemopreventive agents to identify the mechanism of action of these newly discovered bioactive compounds.[65]

Goniothalamin (GTN)

Also known as Pokok Mempisang, is a natural styryl lactone that demonstrates cytotoxic and anti-proliferative activities against diverse cancer cell lines.[66] Goniothalamin (GTN) also possesses important antifungal, antimicrobial, and insecticidal properties.[67] For instance, in H400 oral cancer cells, GTN exhibited selective cytotoxic effects and induced apoptosis via a mitochondrial-mediated pathway associated with the depolarisation of Matrix Metallopeptidases (MMP), releasing cytochrome c into the cytosol and further activating caspases 3/7 and 9. This form of apoptosis was closely associated with the regulation of Bcl-2 family proteins, the S-phase cell cycle arrest, and Nuclear Factor Kappa B (NF-κβ) inhibition.[68] Moreover, GTN significantly inhibited cell proliferation of Ca9-22 oral squamous cancer cells. Apoptosis of GTN-treated Ca9-22 cancer cells revealed an increase in the sub-G1 population and annexin V-intensity. Furthermore, GTN-induced growth inhibition and apoptosis influenced the downstream cascade including reactive oxygen species (ROS) induction, DNA damage, and mitochondria membrane depolarisation.[69] GTN instigate apoptosis either by a direct effect on DNA or by DNA impairment upon oxidative stress while GTN wanes GSH and boosts up ROS production. Alternatively, GTN may target mitochondria directly leading to ROS production. Cellular stress induced by GTN leads to P53 upregulation accounting for the apoptotic initial signal. Furthermore, activated P53 triggers the discharge of Cytochrome c, followed by Caspase-3 and Caspase-9. These caspase dependant pathways entail apoptosis (Fig. 1).

Potentilla discolour

Potentilla discolour of the Rosaceae family is commonly used in the preparation of traditional Chinese medicine that can clinically treat diabetes.[70] Flavonoids and triterpenoids were reported as typical chemical constituents of *Potentilla discolor*.[71] Flavonoids have been recognised to be involved in a wide range of biological activities, including free radical scavenging, apoptosis induction, cancer chemoprevention, and protection from vascular disease.[72] A methanol extract of *Potentilla discolor* (MEPD) induced apoptosis in human mucoepidermoid carcinoma (MEC) cell lines of salivary glands. In addition, MEPD markedly suppressed growth and induced apoptotic cell death in MC3 and YD15 cells. As depicted in (Fig. 2), MEPD treatment significantly upregulated the expression of p53 upregulated modulator of apoptosis (PUMA) and reduced signal transducers and activators of transcription 3 (STAT3) phosphorylation.[73]

Cranberry

Cranberry has been reported to have anti-cancer properties due to its rich content of anthocyanins, flavonoids, and phenolic acids which trigger some of the key apoptotic regulators in oral cancer cells (Fig. 3) (Fig. 4) (Fig. 5).[74] It was previously demonstrated that cranberries possess anti-oxidative, anti-inflammatory, and anti-proliferative properties.[75] A total polyphenol extract containing a variety of flavonoids reportedly inhibited the proliferation of CAL27

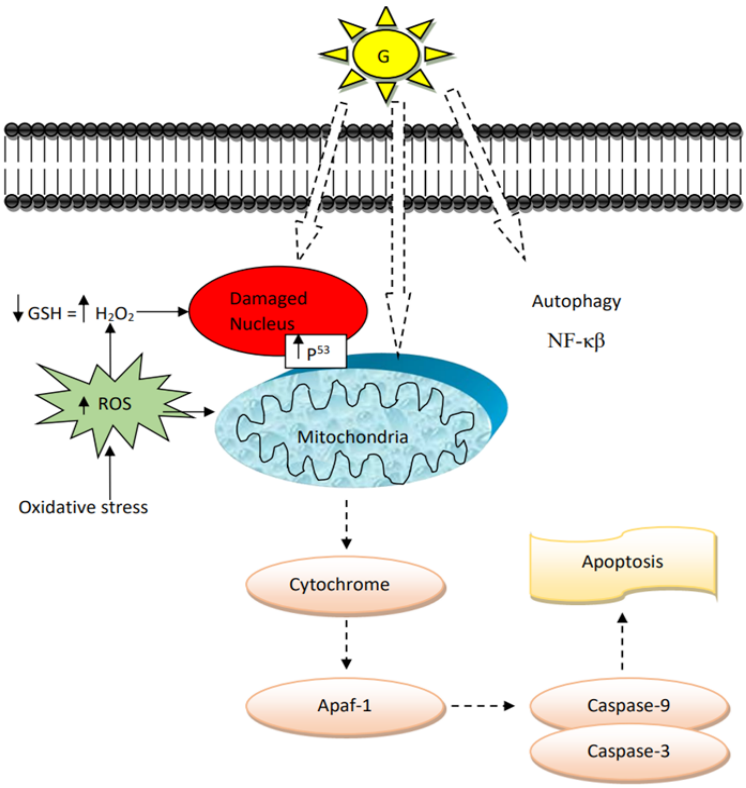

Fig. 1. Schematic illustration of GTN's mechanism of action in cancer cells.

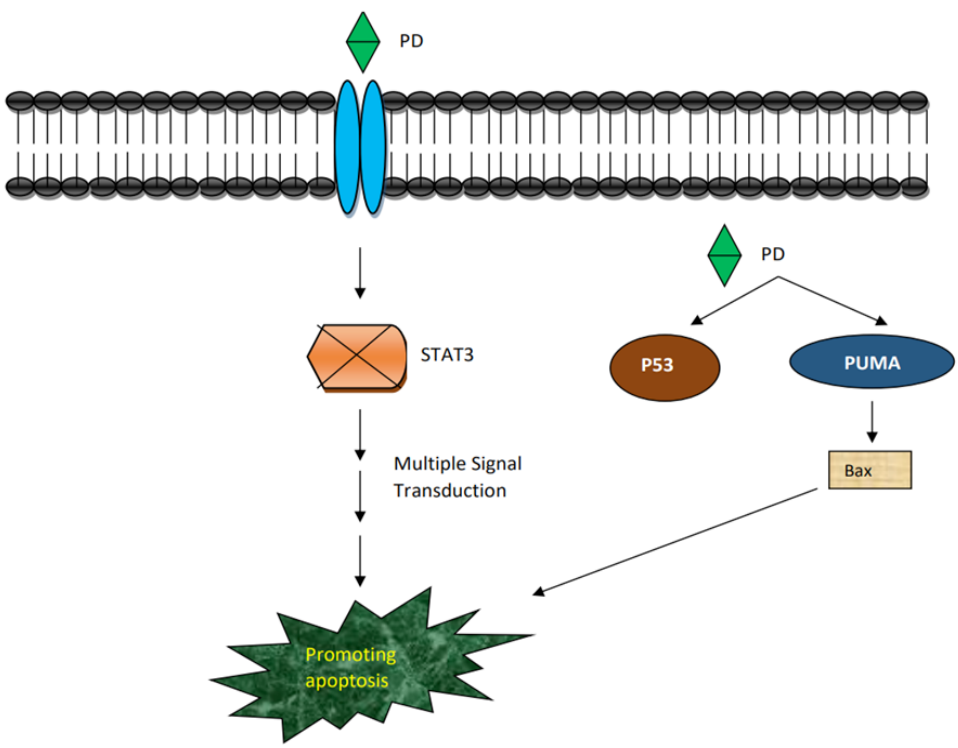

Fig. 2. Schematic illustration of the mechanism of action of *Potentilla discolor* (PD).

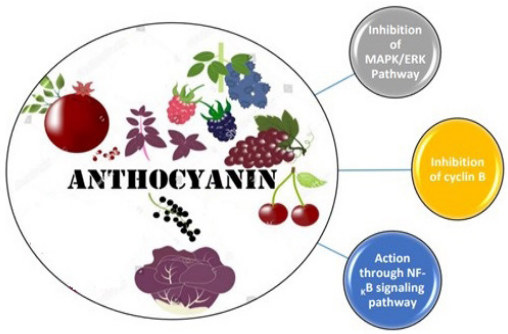

Fig. 3. Mechanism of action of *Anthocyanin*. AP-1 is inhibited by the B-ring of anthocyanin resulting in cell transformation. The compound blocks MAPK/ERK signalling pathway and caspases 3, 7, and 8 to trigger apoptosis. In addition, anthocyanins act on p51 and p21 signalling pathways to inhibit cyclin-B resulting in cell cycle arrest. Furthermore, anthocyanins act on NF-kB mediated signalling pathways to impose anti-inflammatory effects. NF-kB: nuclear factor-kB; MAPK: mitogen-activated protein kinase; ERK: Extracellular signalling regulated kinases.

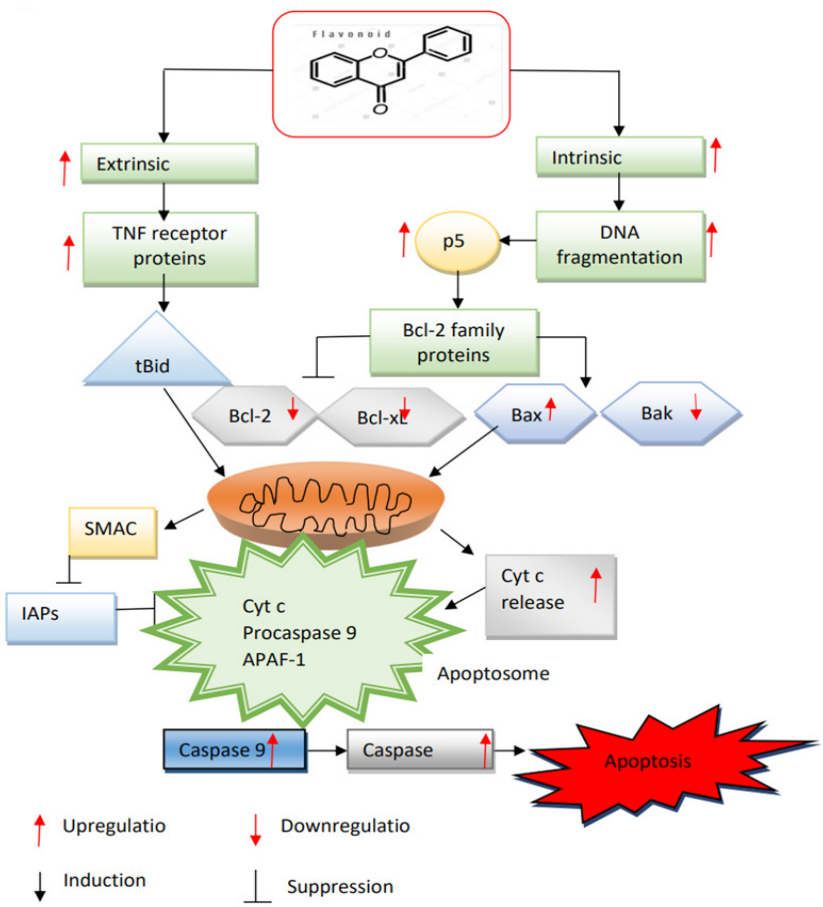

Fig. 4. Schematic representation of the mechanism of action of *flavonoids*. Flavonoids target both extrinsic and intrinsic apoptotic signalling pathways. The extrinsic pathway is related to tumour necrosis factor (TNF) with a special signalling protein, caspase 8. The intrinsic pathway is mitochondrial-mediated where Bcl-2 family proteins activate peculiar caspases 3, 7, and 9. Flavonoids target these apoptotic cascade signalling pathways leading to cancerous cell death. TNF: tumour necrosis factor; tBid: truncated Bid; Bcl-2: B-cell lymphoma protein, Bcl-xL: Bcl-2 variant; Cyt c: Cytochrome c; SMAC: second mitochondrial activator of caspases; IAPs: Inhibitor of apoptosis proteins; APAF-1: Apoptosis protease activating factor 1. Red arrows depict the effects of flavonoids.

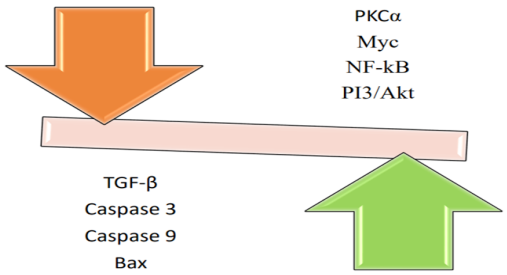

Fig. 5. The molecular mechanism involved in anticarcinogenic activities of *polyphenols*. Polyphenol downregulates the expression and activity of PKCα. Myc, and NF-kB. It stimulates apoptosis by targeting PI3/Akt kinases that result in attenuating Bcl-2 proteins downstream. It can upregulate the TGF-β (tumor suppressor gene), caspases 3, 9, and Bax that trigger apoptosis.

and KB oral cancer cell lines. Meanwhile, anthocyanin and proanthocyanidin sub-fractions were less effective in the oral cell lines compared to the total polyphenolic extract.[76] The proliferation of CAL27 and SCC25 oral cancer cell lines was significantly inhibited by the dose-dependent administration of cranberry extract. The key regulators of apoptosis, caspase-2 and caspase-8, were concomitantly upregulated by the extract.[77]

Green tea

Green tea, from the plant *Camellia sinensis*, contains four major polyphenols: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), epigallocatechin-3-gallate (EGCG), that exhibit chemopreventive activities.[78] Both cell proliferation and migration of H400 and H357 oral cavity cancer cells are transiently inhibited by EGCG. This effect is associated with a decrease in the expression of phosphorylated epidermal growth factor receptor (EGFR).[79] This effect was reported in a study conducted by Payne *et al*. (2022)[80] regarding the effect of EGCG and curcumin on oral cancer cell lines. Resultantly, EGCG blocking cell division was detected in the Gap 1 (G1) phase while curcumin blocking cell division was seen in the Synthesis/DNA damage checkpoint (S/G2M) phase. EGCG exhibited anti-proliferative activities on tumour cells through the blockage of growth factors binding to receptors and the suppression of mitogenic signal transduction.[80] Likewise, EGCG inhibited Hepatocyte Growth Factor (HGF)-induced cell proliferation, migration, invasion, induction of apoptosis, and modulated the HGF/c-Met signalling pathway in the KB oral cancer cell line[81,82] also reported that EGCG inhibited the phosphorylation of Human Epidermal Growth Factor Receptor 2 (HER-2) and hypermethylation of the Reversion-inducing-cysteine-rich Protein with Kazal Motifs (RECK) gene, enhanced the expression of RECK Messenger Ribonucleic Acid (mRNA), and suppressed MMP-2, -9, and urokinase plasminogen activator expression in a dose-dependent manner. Mechanism of action of EGCG is illustrated in (Fig. 6).

Convallaria keiskei (MECK)

Lily of the valley, also known as *Convallaria keiskei* (MECK), is a popular ornamental garden plant and has medicinal value.[83] It has been reported to contain cardenolide glycosides, such as convallatoxin and convallatoxol.[84] Convallatoxin, a cardenolide glycoside extracted from the lily of the valley, is capable of inducing autophagic and apoptotic cell death in several cancer cell lines.[85] A previous study found that MECK significantly inhibited salivary gland cancer growth. At the molecular level, MECK dramatically reduced myeloid cell leukaemia-1

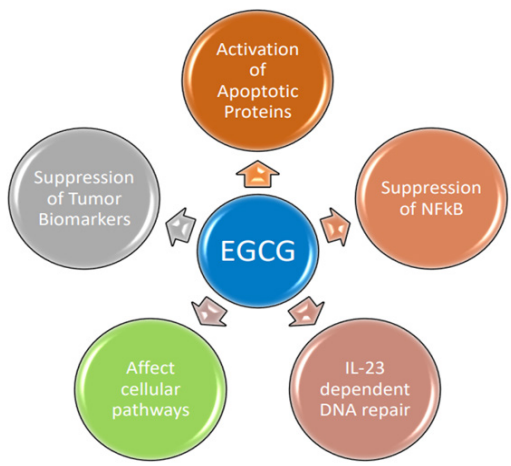

Fig. 6. Molecular mechanisms of action of EGCG. EGCG promotes the arrest of cancer cell growth and induces apoptosis by modifying cell cycle regulatory proteins, stimulating various killer caspases, and suppressing NF-kB. It also promotes IL-dependent repairment of DNA. Besides, it modulates biological pathways including mitogen-activated protein kinase (MAPK) dependent pathway and ubiquitin/proteasome degradation pathway. Furthermore, it suppresses the expression of biomarkers including PI3K, PKA, PKB, c-fos, c-jun, c-myc, res, raf, and cdks.

(Mcl-1) in a translation-dependent manner and induced apoptosis through Bax/Bid. Furthermore, Mcl-1 could be a potential therapeutic target of MECK-induced apoptosis and its stability is regulated by extracellular signal-regulated kinases 1/2 (ERK1/2) signalling.[86]

Geraniin

Geraniin is a dehydroellagitannin found in geraniums and is regarded as the main active compound in various medicinal plants.[12] Scientifically, geraniin has been reported to demonstrate various bioactive properties including anti-hypertensive, anti-hyperglycaemic, anti-cancer, and hepatoprotective.[87] Several mechanisms of action have been postulated to describe the anti-cancer properties of geraniin.[88] Geraniin inhibited the migration and invasion of human oral cancer cell lines SCC-9 and SCC-14 reduced the activity and expression of matrix metalloproteinase-2 (MMP-2) of cancer cells and suppressed the phosphorylation of focal adhesion kinase (FAK), Src, and extracellular signal-regulated kinase (ERK)1/2 (Fig. 7).[89]

Safflower seed

Safflower seed contains acacetin, a substance capable of inducing apoptosis and possessing anti-peroxidative, anti-inflammatory, anti-plasmodial, and anti-proliferative effects by blocking cell cycle progression.[90] Acacetin inhibited the growth of OSCC, and HSC-3, via the cell apoptosis process, determined the cell cycle, increased the sub-G1 population, and decreased the S/M phase. Apoptosis is also involved in caspase signal transduction and mitochondrial stress, which are regulated by ERK and p38.[91] A recent study reported that 12.5- to 200- μM acacetin inhibited cell viability in a dose- and time-dependent manner in 22B cells, a squamous cell carcinoma cell line but a relatively higher concentration was required for oral ACC cells. Furthermore, acacetin promoted the release of mitochondrial cytochrome c release and the process of caspase-9 and caspase-3.[92] Another active constituent of safflower is the safflower polysaccharide (SPS). It inhibits the development of tongue squamous cell carcinoma (TSCC) by regulating the expression of Bcl-2, COX-2, Bax, and cleaved caspase-3 (Fig. 8).[93]

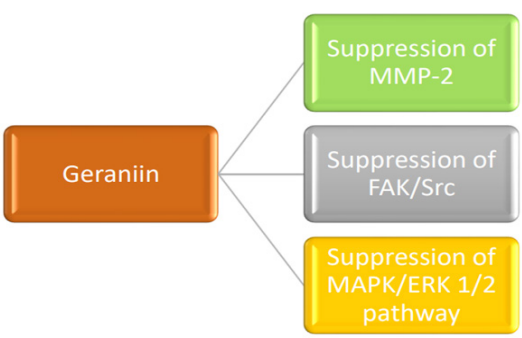

Fig. 7. Mechanism of action of *Geraniin*. Geraniin potently reduces the expression of matrix metalloproteinase-2 (MMP-2), phosphorylation of focal adhesion kinase (FAK), and mitogen-activated protein kinase/extracellular regulatory kinase ½ (MAPK/ERK1/2).

Hedychium coronarium

Hedychium coronarium of the Zingiberaceae family, popularly known as butterfly ginger, butterfly lily, cinnamon jasmine, garland flower, and ginger lily, is a medicinal plant that has exhibited potential cancer chemopreventive activity.[94] One of the most typical natural products purified from *H.coronarium* is the labdane-type diterpene, Coronarin D (CD)[95,96] reported that CD possesses anti-inflammatory, anti-bacterial, and cytotoxic effects. Subsequent studies revealed that CD potentially inhibits the proliferation of 5FU-resistant human oral cancer cells by regulating the Mitogen-Activated Protein Kinase (MAPK) pathway, thereby inducing cell cycle arrest and apoptosis.[97] Likewise, CD strongly increased the c-Jun N-terminal Kinases (JNK1/2) Likewise, CD strongly increased the c-Jun N-terminal Kinases (JNK1/2) phosphorylation and activation of caspase-3, caspase-8, caspase-9, which are indicator proteins of cell apoptosis in the mitochondrial pathway (Fig. 9).[98]

Conclusion

Natural products have been widely used in developing oral anti-cancer drugs. Most of these natural products present bioactive chemical agents and novel mechanisms of action, such as the inhibition of tumour cell growth, the induction of apoptosis, DNA damage, and the inhibition of topoisomerases I and II. Specific activities, such as smoking, alcohol consumption, betel nut chewing, and human papillomavirus infection are risk factors for oral cancers, particularly OSCC. Research on natural products has been increasingly important in the drug discovery field due to their safety profile in toxic studies as opposed to conventional treatment of surgery, chemotherapy, radiotherapy, and targeted drug therapy which have short- and long-term side

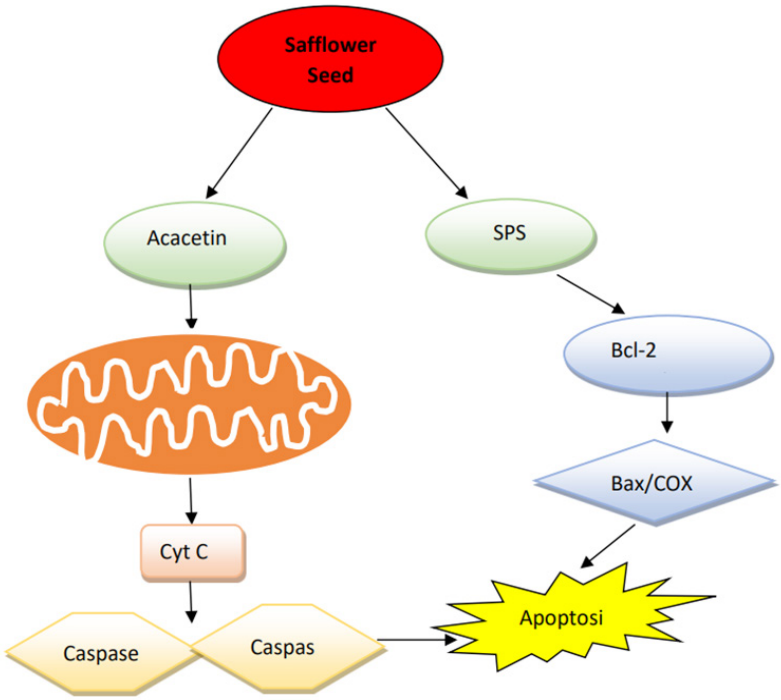

Fig. 8. Molecular mechanism of action of Safflower.

effects. Hence, natural products are also viewed by researchers as alternatives to synthetic drugs. In this review, several natural products have been reported to possess chemopreventive agents that inhibit the cell cycle and induce apoptosis of oral cancer cells line including Goniothalamus, *Potentilla discolor* of the Rosaceae family, cranberry, green tea, lily of the valley, geranium, safflower seeds, and butterfly ginger. Each of these natural products has specific mechanisms of action. In conclusion, this comprehensive review highlights the potential of natural products as chemopreventive agents against oral cancer, emphasising their diverse mechanisms of action and paving the way for future research and clinical trials aimed at harnessing their therapeutic benefits.

Limitations and Future Direction

Although natural products hold promise as potential chemopreventive agents, their efficacy and safety profiles need to be rigorously evaluated through well-designed clinical trials. Many studies conducted so far have been limited to preclinical models, and there is a lack of robust evidence from human trials to support their clinical use. Additionally, the bioavailability and pharmacokinetics of natural compounds may

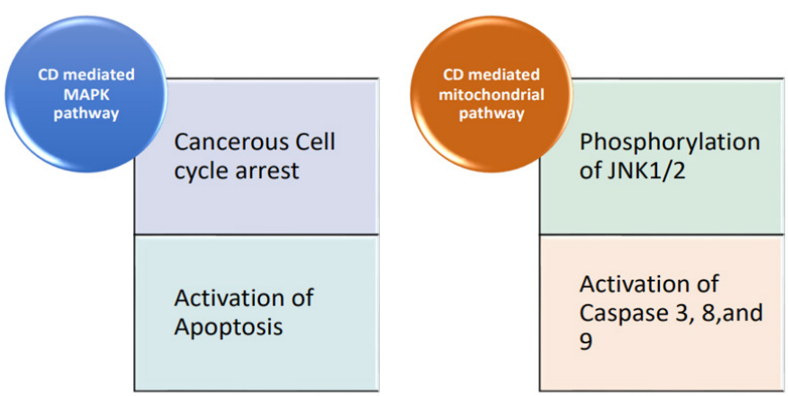

Fig. 9. Molecular mechanism of action of Coronarin D (CD).

vary, posing challenges in achieving therapeutic concentrations at the target site. Furthermore, the mechanisms of action of many natural products remain incompletely understood, hindering the development of targeted therapies and personalised treatment strategies. Moreover, the synergistic or antagonistic effects of combining different natural products or integrating them with conventional therapies require further investigation.

In the future, there is a need to address these limitations through interdisciplinary research efforts. A well-designed clinical trial is needed to evaluate the efficacy, safety, and optimal dosing regimens of natural products in preventing oral cancer development and progression. These trials should incorporate biomarker analyses and patient stratification to identify responders and non-responders. Advanced analytical techniques, such as metabolomics, proteomics, and transcriptomics, can be employed to elucidate the molecular mechanisms underlying the chemopreventive effects of natural products. Furthermore, innovative drug delivery systems, such as nanoparticles and liposomes, can enhance the bioavailability and tissue specificity of natural compounds, improving their therapeutic efficacy. Moreover, the development of nutraceuticals and dietary supplements containing standardised formulations of natural products holds promise for promoting oral health and preventing oral cancer in high-risk populations. Collaborative efforts between researchers, clinicians, industry partners, and regulatory agencies are crucial for translating preclinical findings into clinical practice and ultimately reducing the global burden of oral cancer.

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