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A Review of Promising Natural Chemopreventive Agents for Head and Neck Cancer

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Abstract

Head and neck squamous cell carcinoma (HNSCC) accounts for 300,000 deaths per year worldwide and overall survival rates have shown little improvement over the past three decades. Current treatment methods including surgery, chemotherapy, and radiotherapy leave patients with secondary morbidities. Thus, treatment of HNSCC may benefit from exploration of natural compounds as chemopreventive agents. With excellent safety profiles, reduced toxicities, antioxidant properties, and general acceptance for use as dietary supplements, natural compounds are viewed as a desirable area of investigation for chemoprevention. Though most of the field is early in development, numerous studies display the potential utility of natural compounds against HNSCC. These compounds face additional challenges such as low bioavailability for systemic delivery, potential toxicities when consumed in pharmacological doses, and acquired resistance. However, novel delivery vehicles and synthetic analogs have shown overcome some of these challenges. This review covers eleven promising natural compounds in the chemoprevention of HNSCC including vitamin A, curcumin, isothiocyanate, green tea, luteolin, resveratrol, genistein, lycopene, bitter melon, withaferin A, and guggulsterone. The review discusses the therapeutic potential and associated challenges of these agents in the chemopreventive efforts against HNSCC.

Keywords

head and neck cancer; squamous cell carcinoma; natural compounds; prevention; curcumin; vitamin

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the United States and accounts for more than 300,000 deaths per year worldwide (1). Despite numerous therapies, HNSCC is associated with poor overall survival rates (<50%) that have not improved significantly within the last 30 years.

Exposure to tobacco, alcohol, and numerous other environmental factors can result in field cancerization (1). More recently, HNSCC has been linked to human papilloma virus (HPV) infection. Cessation of exposure to carcinogens is an effective way to decrease incidence of HNSCC. However, this is not always an effective means of prevention as genetic alterations caused by initial carcinogen exposures can ultimately lead to transformation long after cessation (1). Standard therapeutic approaches such as surgical intervention, radiation, and chemotherapy are effective in a limited subgroup of patients and often result in additional morbidities. Therefore, there is a great need for prevention and early diagnosis of high-risk premalignant lesions (2). Chemoprevention is defined as the use of natural or synthetic substances to reverse, suppress, or prevent the initiation, promotion, or progression of cancer (2).

Use of natural compounds for chemoprevention is highly compelling due to their safety, low toxicity, and general acceptance as dietary supplements (3). These natural dietary agents hold great promise for chemopreventive use due to their ability to decrease the occurrence of cancer (3). However, there are many associated challenges with the use of natural compounds. Some have increased toxicities or low bioavailability and may trigger resistance mechanisms, all of which are accentuated by using these compounds in pharmacological doses (2). For chemoprevention to be feasible in premalignant populations, the compound must be well-tolerated and have long-lasting benefit. Moreover, the various signaling pathways contributing to HNSCC tumorigenesis mandate use of compounds with multiple molecular targets (2).

Several approaches including development of synthetic analogs, adding bioadjuvant compounds to conventional therapies, using nanoparticles and other delivery agents to improve bioavailability, increasing solubility using phospholipid complexes, show promise in overcoming these challenges (4–6). In this review, we highlight natural compounds with the most potential as chemoprevention agents against HNSCC (Figure 1).

Vitamin A

Vitamin A is a fat-soluble vitamin that is the first and best studied natural chemopreventive compound tested in HNSCC. Analogues of vitamin A, such as retinoids or carotenoids, can be found in liver, fish oil, milk, eggs, and various fruits and vegetables. Several clinical studies have looked at the effect of various vitamin A derivatives on oral premalignancies, second primary tumors, and survival rates (Table 1).

Clinical highlights

In 1986, Hong et al. were the first to study isotretinoin (13-cis-retinoic acid), a vitamin A derivative, as a treatment for oral leukoplakia (7). The study showed effectiveness of isoretinoin in decreasing the size of lesions and reversing dysplasia in patients by 67% and 54%, respectively, when compared to placebo. Isoretinoin is also effective in patients with oral premalignancies and in preventing recurrences among HNSCC patients who were disease-free after first-line therapy (surgery, radiotherapy, or both) (8). While there were no differences in recurrence of primary cancers, isoretinoin significantly reduced second primary tumors (SPT) in a dose-dependent manner (9). In each study, isoretinoin induced mild to severe toxicity. Retinyl palmitate and β-carotene are precursors of vitamin A that demonstrated efficacy and minimal toxicity in premalignant lesions (10).

A more recent study compared therapeutic effects of isoretinoin with retinyl palmitate and β-carotene in patients with HNSCC (11). Treatment with isoretinoin had a greater clinical response than the combination of retinyl palmitate with β-carotene or retinyl palmitate alone. However, toxicity remained a significant issue with isoretinoin as six patients left the study from toxicity-related issues. Moreover, the study found no significant association between oral premalignant lesion response and survival.

Synergistic interactions

Isoretinoin in combination with interferon-α and α-tocopherol (vitamin E) demonstrates the most promise in chemoprevention of oral premalignancies (Table 2). Vitamin E decreases isoretinoin toxicity in addition to having possible chemopreventive effects (12). There has been significant response against laryngeal lesions and advanced dysplasia (6). Further, there has been therapeutic benefit from isoretinoin with surgery or radiotherapy in HNSCC patients with advanced disease (13). A follow-up study confirmed the promising results with longer survival rates and fewer incidence of SPT (12). Mild to moderate toxicity, though manageable, was still observed in these patients (12,13).

Future considerations

The use of vitamin A derivatives, such as isoretinoin, has long been proven an effective means of chemoprevention in HNSCC. However, toxicity remains a limitation to the utility of the vitamin A derivatives in patients (Table 3). Use of bioadjuvant therapy, such as vitamin E, may improve associated toxicity, though phase 3 trials are still ongoing (12). Developing novel strategies for delivering these compounds to directly the tumor site could further reduce toxicity in patients.

Curcumin

Turmeric, derived from the rhizomes of *Curcuma longa*, is used as a spice and, particularly in Asia, as a treatment for a number of ailments. Commercially available, turmeric is usually a mixture of three curcuminoids, curcumin (72%), demethoxycurcumin (19%), and bisdemethoxycurcumin (9%). Curcumin, also called diferuloyl methane or bis-a,b-unsaturated b-diketone, is a yellow, hydrophobic polyphenol that has been widely

investigated for its antitumor effects in multiple cancer types (2). The major challenge with curcumin lies with its low bioavailability due to limited absorption from the gut.

Several novel packaging strategies including liposomes, polymer nanoparticles, nanogels, and micelles have improved the bioavailability of curcumin (14). Analogs of curcumin also greatly increase the bioavailability, potency, and stability (4,5,15,16). In addition, encapsulation of curcumin and its analogs by lipids and nanoparticles greatly increases bioavailability (17).

Molecular targets and mechanisms of action

Curcumin's anticancer effects mainly result from its various pro-apoptotic and anti-inflammatory effects. Curcumin induces apoptosis via a number of molecular mechanisms. It causes cell cycle arrest, inhibits proliferation in HNSCC, via upregulation and activation of p53 and p21 (18,19).

Curcumin has anti-inflammatory effects that can work to prevent the development and progression of cancer. Curcumin downregulates nuclear factor-B (NF-κB) and mitogen activated protein kinase (MAPK) pathways, which prevent expression of pro-inflammatory cytokines and cell signaling necessary for proliferation, metastasis, and angiogenesis (19). Specifically, curcumin-mediated NF-κB inhibition mitigates the expression of proinflammatory cytokines IL-6 and IL-8. These cytokines are upregulated in patients with HNSCC compared to controls (20). Moreover, curcumin inhibits tumor growth by targeting the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) (21) (Figure 2).

Clinical highlights

The first clinical trial investigating turmeric and curcumin as anti-cancerous agents used a one percent curcumin ointment on skin cancer lesions. Reduced pain and lesion size were reported in 10% percent of patients (22). A more recent phase I clinical trial conducted showed histological improvements of precancerous lesions in oral cancer patients upon treatment with curcumin, which was not toxic even at doses of 8000 mg/day (23) (Table 2). However, this trial also clearly showed that curcumin exhibits poor bioavailability, having a mere 1% absorption rate upon oral administration (23). The low plasma and tissue levels of curcumin result from poor absorption due to reduced solubility in water as well as rapid systemic elimination (17).

Synergistic interactions

The chemopreventive effects of curcumin greatly increase when used concomitantly with other natural agents including piperine, genistein, green tea, or embelin. Curcumin also synergistically increased the efficacy of several chemotherapeutic agents including cisplatin, 5-fluorouracil (5-FU), vinca alkaloid, vinorelbine, and gemcitabine (24).

Future considerations

The use of curcumin as a chemopreventive agent in HNSCC is promising due to its effect on multiple molecular pathways essential for cancer progression. Moreover, studies suggest

efficacy in combining curcumin with radiation therapy as a first line of treatment in HNSCC (25). Although bioavailability remains a challenge, there are numerous viable approaches to circumvent this problem. Natural derivatives including difluorinated-curcumin (CDF), diphenyl difluoroketone (EF24), and 3, 5-bis (2, 4-difluorobenzylidene)-4-piperidone (DiFiD) also seem to have promise for use in HNSCC as they have been shown to exhibit tumor growth inhibition and increased metabolic stability compared to curcumin in other tumor types (26,27).

Isothiocyanates

Cruciferous vegetables, including broccoli, kale, and watercress, have various anti-cancer properties due to high glucosinolate content. Isothiocyanates (ITCs) are the most potent component of glucosinolates when isolated via enzymatic hydrolysis. Phenethyl isothiocyanate (PEITC), benzyl isothiocyanate (BITC) and sulforaphane are three naturally occurring ITCs that are being studied as chemopreventive agents (28).

Molecular targets and mechanisms of action

ITCs cause apoptosis and prevent activation of the NF-κB signaling pathway via numerous mechanisms. PEITC and sulforaphane inhibit NF-κB transcriptional activity by through multiple methods including preventing dimerization of the molecule and other downstream effects (29). BITC acts to inhibit NF-κB phosphorylation, inducing apoptosis in target cells (30). PEITC also works upstream to decrease EGFR phosphorylation to inactivate NF-κB.

Furthermore, by decreasing EGFR signaling, PEITC can suppress the expression and enzymatic activities of matrix metalloprotease-2 (MMP-2) and MMP-9 (31). MMPs cause extracellular matrix degradation, facilitating tumor metastasis. Both MMP-2 and -9 are expressed in oral cancer and are associated with tumor invasion. BITC induced apoptosis in five HNSCC lines and upregulated anti-proliferative activity in cell lines (32).

Clinical highlights

Preclinical trials showed PEITC reduced growth of oral cancer by inducing apoptosis in cancer cells (33). Furthermore, topical application of ITCs induced strong chemopreventive activity against HNSCC in animal models (34). A more recent study demonstrated that ITCs, specifically BITC, inhibit HNSCC migration and invasion. In addition, BITC increased sensitivity to cisplatin treatment *in vitro*, enhancing the effects of chemotherapy (35). Sulforaphane down-regulated various MMPs in HNSCC cell lines, which makes it a potential inhibitor of metastasis (28). A pilot clinical trial using broccoli sprout extracts in ten healthy volunteers demonstrated target modulation at low micromolar doses in the oral mucosa on oral administration indicating adequate bioavailability, though further investigation is warranted (36).

Future considerations

ITCs hold great potential as chemopreventive agents due to ease of integration into patient diets. However, it has been difficult for researchers to create formulations of pure ITCs suitable for clinical investigation and small changes in their molecular formulas drastically

change the mechanisms of action. As clinical trials continue, use of ITCs as adjuvant therapy to conventional anticancer agents seem especially promising due to the substantial increase in efficacy when used in combination (Table 3).

Green tea

Tea is a widely-consumed beverage rich in substances with antioxidant properties. Studies exist investigating both black and green tea as chemopreventive agents, though green tea shows greater efficacy against multiple types of cancer. The health effects of green tea are mostly associated with its polyphenol (PP) content. PPs are reactive metabolites characterized by several hydroxylated aromatic groups and possess powerful antioxidant activity by scavenging a wide range of reactive oxygen, nitrogen, superoxide anions and metal ions. Green tea extract (GTE) contains four major polyphenols: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) (38) (Table 1). EGCG is the most abundant polyphenol in green tea and has gained the most attention in anti-carcinogenic studies (2).

Molecular targets and mechanisms of action

EGCG has several mechanisms of action, but its antitumor effects stem primarily from suppression of EGFR phosphorylation (39,40). Up to 90% of HNSCC patients show EGFR overexpression, suggesting GTE could be effective in chemoprevention. EGCG also acts downstream of EGFR to inhibit protein kinase B (Akt) phosphorylation and eventually activation and nuclear translocation of NF-κB (40).

GTE inhibits the vascular endothelial growth factor receptor (VEGFR) activation and VEGF secretion, reducing angiogenesis (40,41). This is a result of inhibition of NF-κB by EGCG (41). EGCG also acts to suppress the MAPK signaling pathway, preventing the transcription of MMPs, specifically MMP-2 and 9, which are expressed in oral cancers (42).

Clinical highlights

Preclinical investigation of GTE chemoprevention started in 1987 with a study that showed topical application of EGCG inhibited tumor formation in mice (43). More recent studies confirm that oral intake of EGCG-rich GTE inhibit cancer development and metastasis in mice models *in vitro* and *in vivo* (44). EGCG specifically prevented growth of HNSCC cell lines and enhanced effects of 5-fluorouracil (39).

Several phase I trials show similar antitumor effects in humans (45). According to a phase I trial, a dose of 1.0 g TID, equivalent to 7 or 8 cups of green tea, could safely be consumed by patients (46). In patients with high-risk oral premalignant lesions, high-dose GTE for 12 weeks led to higher clinical response rates but showed no significant improvement in cancer-free survival, indicating the need for further studies. Poor bioavailability was reported in the majority of patients in phase II clinical trials (47) (Table 2). The study also assessed the pharmacokinetics of EGCG in the plasma with 500 or 1000mg/m2 of oral, thrice daily GTE dosing. Free EGCG accounted for only 12-28% of total EGCG possibly due to poor oral absorption of EGCG.

Synergistic interactions

Multiple synergistic interactions involving GTE have been investigated with some continuing to clinical trials. In preclinical studies, GTE increased the efficacy of many compounds including luteolin, genistein, atorvastin, curcumin, erlotinib, sulindac, tamoxifen, celecoxib, cisplatin, adriamycin, dacarbazine, lycopene, and EGFR inhibitors in the inhibition of HNSCC growth (3,40). EGCG also sensitizes multidrug-resistant forms of HNSCC to vincristine sulfate, decreasing tumor growth via down-regulation of VEGF *in vitro* (48). The combination of erlotinib and GTE created a synergistic effect in mice and is currently being studied in a phase 1 chemoprevention study on patients with premalignant lesions of the head and neck (1).

Future considerations

The use of GTE as a chemopreventive agent in HNSCC seems promising and warrants further studies. There are very few associated toxicities, many synergistic effects, and clear chemopreventive benefit. However, there is a need to improve the bioavailability, standardize the different formulations of GTE, and investigate the effects of greater dosages over longer periods of time (47). Nanoparticle-mediated EGCG delivery enhances bioavailability and reduces toxicity, thus providing an alternate route for EGCG use (49) (Table 3).

Luteolin

Luteolin is flavonoid, a group of PPs that are found in vegetables like cabbage, celery, broccoli, and parsley. Plants rich in flavonoids have been used in traditional East Asian medicine for their anti-inflammatory effects (50). The anti-cancer effects of luteolin are beginning to be investigated, though the exact biological and molecular mechanisms remain somewhat unclear (51).

Molecular targets and mechanisms of action

Luteolin acts to inhibit activation and phosphorylation of Akt, suppressing VEGFR-mediated angiogenesis and downstream activation of NF-κB (52). It is by blocking the NF-κB pathway and subsequent formation of pro-inflammatory cytokines like TNFα and IL-1 that luteolin produces anti-inflammatory effects.

Luteolin causes cell cycle arrest due to decreased CDK4/6 activity. CDK4/6 form a complex with cyclin D1, which is downregulated via suppression of the Akt signaling pathway (53). The Akt pathway plays a major role in cell cycle progression and is often upregulated in many forms of cancer, including HNSCC (54).

Clinical highlights

Preclinical studies showed luteolin causes apoptosis of HNSCC cell lines and inhibits tumor growth in mice (55). A similar study found luteolin decreased both the incidence and tumor volume of lung cancer significantly compared to controls in mice (56). Akt expression was downregulated in a dose-dependent manner in mice. Surprisingly, treated mice showed no decrease in body weight or other cytotoxic effects compared to control mice (55). Delivery of luteolin in nanoparticles significantly inhibited growth of HNSCC tumors *in vitro* and *in*

vivo and showed increased efficacy compared to free luteolin, which displays poor bioavailability due to poor solubility (57). Despite these encouraging results, no clinical trials have begun to investigate luteolin in humans.

Synergistic Interactions

Luteolin improves the cytotoxic effects of many chemotherapy and chemopreventive treatments including cisplatin, doxorubicin, TNF-α, paclitaxel, and EGCG in various types of cancer (58). Preclinical trials for HNSCC show combination treatment of luteolin with paclitaxel enhanced inhibition of tumor growth compared to paclitaxel alone (59).

Future considerations

Luteolin is a natural agent that still requires investigation to be deemed effective in humans. One major obstacle to the clinical application of luteolin is it's low systemic bioavailability due to metabolism in the liver and intestine (3). However, the epithelium of the oral cavity can absorb luteolin directly, and delivery with nanoparticles may solve other problems with bioavailability that may arise (60). However, phase I and II trials investigating the role of luteolin in chemoprevention of any cancers have still not begun.

Resveratrol

The compound resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring phytoalexin found in grapes, peanuts, and mulberries (61). High levels of resveratrol are found in the skin of grapes and in red wine (3). Resveratrol is widely considered the cardioprotective factor in red wine and is being investigated for anti-cancer properties (62).

Molecular targets/mechanisms of action

Resveratrol targets multiple signaling pathways that facilitate cell growth, inflammation, and cell survival. Resveratrol increases expression and activation of p53 and elevation in p21 levels (62). This causes cell cycle arrest and apoptosis in cells. By suppressing phosphorylation of STAT3, resveratrol also inhibits the JAK/STAT pathway of signaling that is constitutively activated in HNSCC cells, causing cell death (63). Furthermore, resveratrol decreases NF-κB activation and nuclear translocation of the p65 subunit in a variety of cell types (62). Resveratrol also acts upstream of NF-κB to suppress Akt activity and signaling (64). In order to reduce inflammation, resveratrol inhibits the MAPK signaling pathway, preventing formation of pro-inflammatory cytokines (18).

Clinical Highlights

Chemopreventive studies involving resveratrol began after 1997 when a study found topical application of the agent prevented tumor formation in mice (65). Subsequent preclinical studies confirmed similar anti-tumor effects in various cancer cell lines, including HNSCC cells (63). One study showed resveratrol inhibited tumor growth in mice, however efficacy of resveratrol in humans proves more complicated to confirm due to poor bioavailability (66). When consumed orally, 70-80% of resveratrol is absorbed by the intestines (67). Further, after administration of 5g daily for 29 days, trans-resveratrol was detected in the plasma at concentrations as high as 4 μM. Mechanisms to increase bioavailability are under

investigation and include packaging within nanoparticles and co-administration with curcumin (68,69). In humans, resveratrol toxicity is minimal, and one phase I study showed even amounts as high as 5 g was safe in healthy patients (3).

Synergistic interactions

Resveratrol has many synergistic interactions with chemopreventive compounds including EGCG, vitamin E, genistein, cisplatin, doxorubicin, fluorouracil (FU), paclitaxel, and curcumin (3). In HNSCC, the combination of resveratrol and curcumin was more effective at inhibiting cancer growth in preclinical models than curcumin alone (70). 5-FU and resveratrol also showed a synergistic antitumor effect in HNSCC cell lines (71,72). Resveratrol enhanced sensitivity to chemotherapy and radiotherapy in HNSCC cells (73).

Future considerations

The use of resveratrol shows promise as a chemopreventive agent against HNSCC, especially when used as adjuvant therapy with other chemotherapeutic agents. Clinical trials are currently underway to further investigate the effects of resveratrol in patients, and studies to increase bioavailability may improve efficacy.

Genistein

The natural compound Genistein (4,5,7-trihydroxyisoflavone) is a phytoestrogen abundant in soybeans and other legumes (3,74). There have been no clinical studies that examine the effects of genistein on HNSCC. Epidemiological studies demonstrated efficacy of genistein intake on breast, prostate, and colorectal cancers (75). However, habitual consumption of soy products showed no significant effect on the risk of HNSCC in Chinese adults, though this study had many significant limitations (76).

Molecular targets/mechanisms of action

Several studies revealed the anti-cancer effects of the consumption of soy products. By affecting multiple pathways, genistein has anti-proliferative and anti-angiogenic effects (3). Genistein significantly downregulates MAPK and Akt signaling, inhibiting VEGF-mediated angiogenesis in HNSCC cells (77). It also acts downstream to inhibit NF-κB and thus cell proliferation (77). Other anti-proliferative effects of genistein result from decreased phosphorylation of the insulin-like growth factor receptor (IGFR) and IGF signaling, inhibiting cell growth (78). Genistein acts to induce cell cycle arrest and apoptosis by activating p53 and increasing p21 expression (79). Secretion of MMP-2 and -9 decreases with genistein, inhibiting tumor invasion and migration capabilities (74).

Clinical Highlights

Despite numerous molecular targets, preclinical trials involving genistein and HNSCC are not conclusive in showing efficacy as a chemopreventive agent. Low concentrations of whole soy protein extract significantly inhibited oral cancer growth in cell lines (80). However, genistein itself varies in its efficacy between studies. One study showed purified genistein had no effect on the tumor growth and metastasis but inhibited tumor invasion (81). A more recent study contradicted previous results, showing genistein inhibited

proliferation of HNSCC cell lines (82), thus necessitating further research to confirm genistein efficacy.

Synergistic interactions

As genistein might have its greatest utility in combination, it has many synergistic interactions with chemopreventive agents including EGCG, letrozole, docetaxel, resveratrol, lycopene, vitamin D, tamoxifen, paclitaxel, cisplatin, erlotinib, gemcitabine, doxorubicin, FU, camptothecin, bleomycin, and cetuximab (83). One study combined cetuximab, an anti-EGFR monoclonal antibody, with genistein to evaluate inhibition of the EGFR pathway. Even at low concentrations, the combination resulted in additive growth inhibition and increased apoptosis compared to single agent exposure (83) (Table 2).

Future considerations

Genistein seems to hold its most promise as an adjuvant therapy. However, further preclinical and eventually clinical studies may prove its efficacy as a single agent in chemoprevention of HNSCC.

Lycopene

The natural compound lycopene is a red-colored carotenoid and is predominantly found in tomatoes (3,84). Of the carotenoids, lycopene is the most abundant in fruits and vegetables and the most promising in chemoprevention. Various epidemiological studies show dietary supplementation with lycopene decreases risk of cancer, and effected molecular targets are numerous and diverse (85).

Molecular targets/mechanisms of action

Lycopene acts at multiple points to inhibit VEGF-mediated angiogenesis. Lycopene suppresses Akt activation by preventing phosphorylation of the molecule (86). Further downstream, lycopene directly inhibits the NF-κB signaling pathway by preventing nuclear translocation and NF-κB DNA binding (87). By decreasing plasma levels and activity of MMP-2 and -9, lycopene also acts to inhibit invasion and metastasis (88).

Clinical highlights

Preclinical studies show that lycopene decreased HNSCC cell growth, induced apoptosis in cells, and prevented tumor invasion (89). Lycopene worked to inhibit the Akt signaling pathway in a dose-dependent manner.

When used in humans, lycopene was safe and more effective in the management of oral leukoplakia in patients than placebo (90). The treatment of oral premalignant lesions with lycopene was associated with significant clinical and histological responses compared with placebo or absence of treatment against HNSCC (91). Lycopene significantly reduced multiple forms of HNSCC including laryngeal, oral, and pharyngeal cancer (91) (Table 2). Phase II trials of lycopene have shown effectiveness in decreasing prostate cancer growth, suggesting it may be useful in prevention and treatment in other forms of cancer (92).

Future considerations

Much preclinical and clinical evidence gives promise to the use of lycopene as an effective chemopreventive agent against HNSCC. There is little associated toxicity, and it shows significant response against other forms of cancer. However, the need exists for more mechanistic studies and randomized controlled trials to confirm the benefits of lycopene and its use in routine prevention and management of HNSCC (84) (Table 3).

Bitter Melon

Bitter melon, which is grown primarily in Asia, Africa, and South America, is a plant that has been used in traditional medicine practices, especially for patients with diabetes, and is beginning to be investigated as a chemopreventive agent. Preclinical studies show that bitter melon extract (BME) inhibited HNSCC growth *in vitro* and *in vivo* in mice by modulating immune regulatory mechanisms (93–95). Exact molecular mechanisms of action are starting to be elucidated, but no clinical trials investigating anti-tumor effects of bitter melon have begun.

Medicinal Plant Compounds

Numerous medicinal plant-derived compounds are being investigated for their anticancer properties. Such compounds include withaferin A, which is extracted from *Vassobia breviflora* in Latin America. Preclinical studies show antiproliferative effects of withaferin A on HNSCC cell lines by interacting with Akt and inducing apoptosis (96). Another such compound is guggulsterone, which is widely available and well-tolerated. Guggulsterone enhances efficacy of chemotherapy drugs including erlotinib, cetuximab, and cisplatin by decreasing expression of STAT-3 (97). These compounds are only two examples of extracts from plants that are in studies for HNSCC treatment, though no clinical trials are in effect.

Conclusion

HNSCC claims more than 300,000 lives each year worldwide, and with poor overall survival rates (<50%) using current therapies. Smoking, alcohol use, and HPV-infection are the largest risk factors for HNSCC, thus primary prevention focuses on mitigating risk factors. Even in lieu of improved management of risk factors, HNSCC will remain dangerous through genetic predispositions and prior field cancerization. As treatment with surgery, chemotherapy, and radiotherapy often cause severe morbidity from damage to the upper aerodigestive tract, the prevention and early diagnosis of high-risk premalignant lesions should be emphasized. The use of natural compounds in the chemoprevention of HNSCC shows promise in reversing these abysmal trends.

Natural compounds show promise as chemopreventive agents in HNSCC because of their tolerability, safety, low toxicity, antioxidant properties, and general acceptance as dietary supplements (3). Moreover, many studies have displayed the potential utility of natural compounds against HNSCC.

Depending on the compound, however, specific challenges exist including low bioavailability, high toxicity, and few molecular targets. There are myriad solutions to

circumvent these problems including the use of chemical analogs, adjuvant therapies, and nanoparticle delivery mechanisms. Currently, this field remains in its infancy and its biggest challenge is a shortage of research on chemopreventive natural compounds specific to HNSCC. In order to find safe and effective compounds, clinical trials must continue for the different natural agents.

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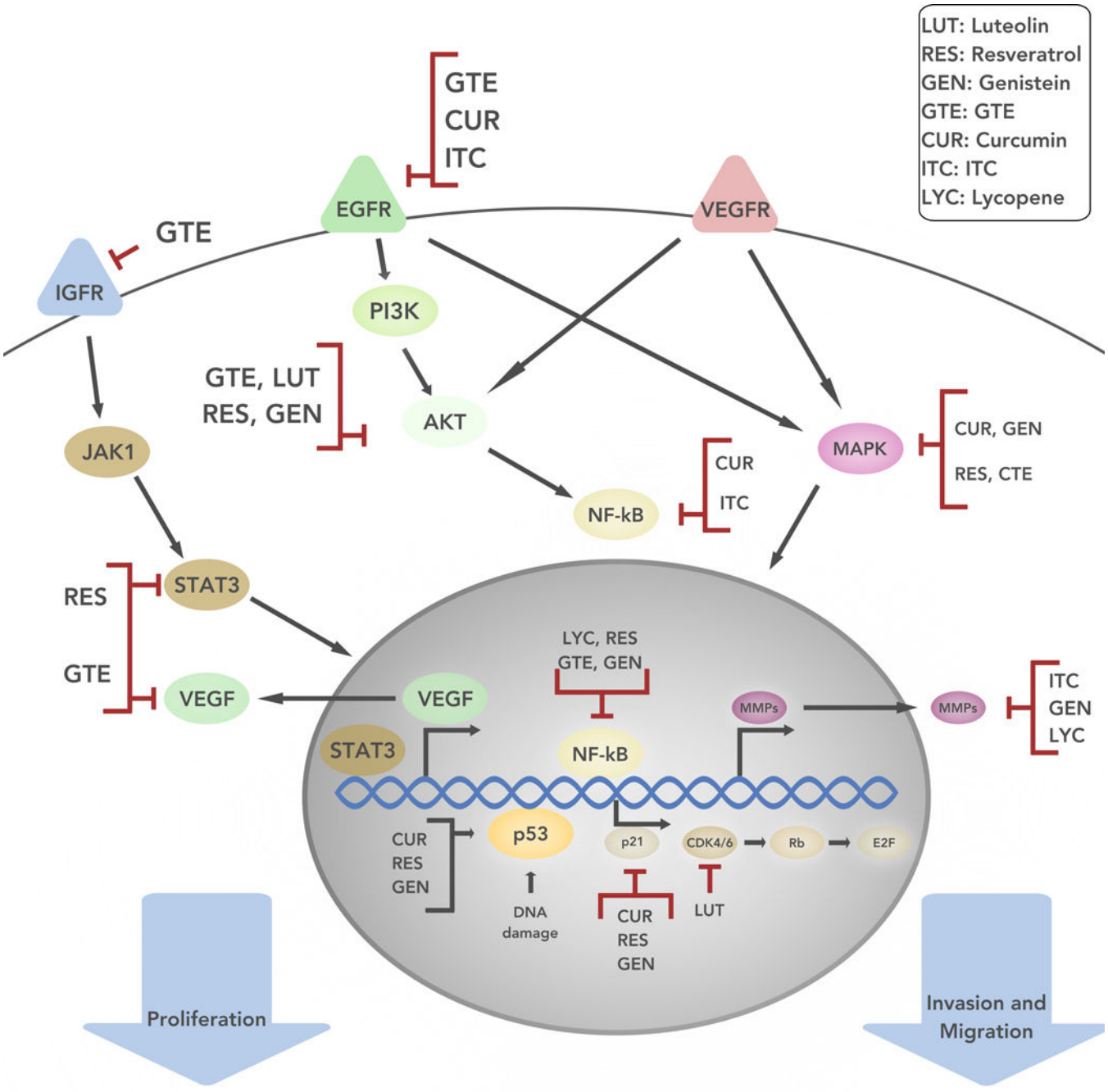

Figure 1.

The schematic represents various signaling pathways that occur within tumor cells, which allow for cell growth, proliferation, and invasion. The arrows between the signaling molecules represent progressions in the pathway. For example, IGFR signals through the JAK/STAT3 pathway to allow for cell proliferation. The natural compounds discussed can promote cell apoptosis (Luteolin, Resveratrol) and/or inhibit cell growth, proliferation, and invasion (Luteolin, Resveratrol, Genistein, GTE, Curcumin, ITCs, Lycopene). IGFR = Insulin-like growth factor 1 receptor; JAK1 = Janus kinase 1; STAT3 = signal transducer and activator of transcription 3; EGFR = epidermal growth factor receptor; PI3K =

phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT = protein kinase B; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; VEGFR = receptors for vascular endothelial growth factors ; MAPK = mitogen-activated protein kinases; VEGF = vascular endothelial growth factor; p53 = tumor protein p53; p21 = cyclin-dependent kinase inhibitor 1; CDK4/6 = cyclin-dependent kinase 4/6; Rb = retinoblastoma protein; E2F = transcription factor coder for eukaryotes; MMPS = matrix metalloproteinases.

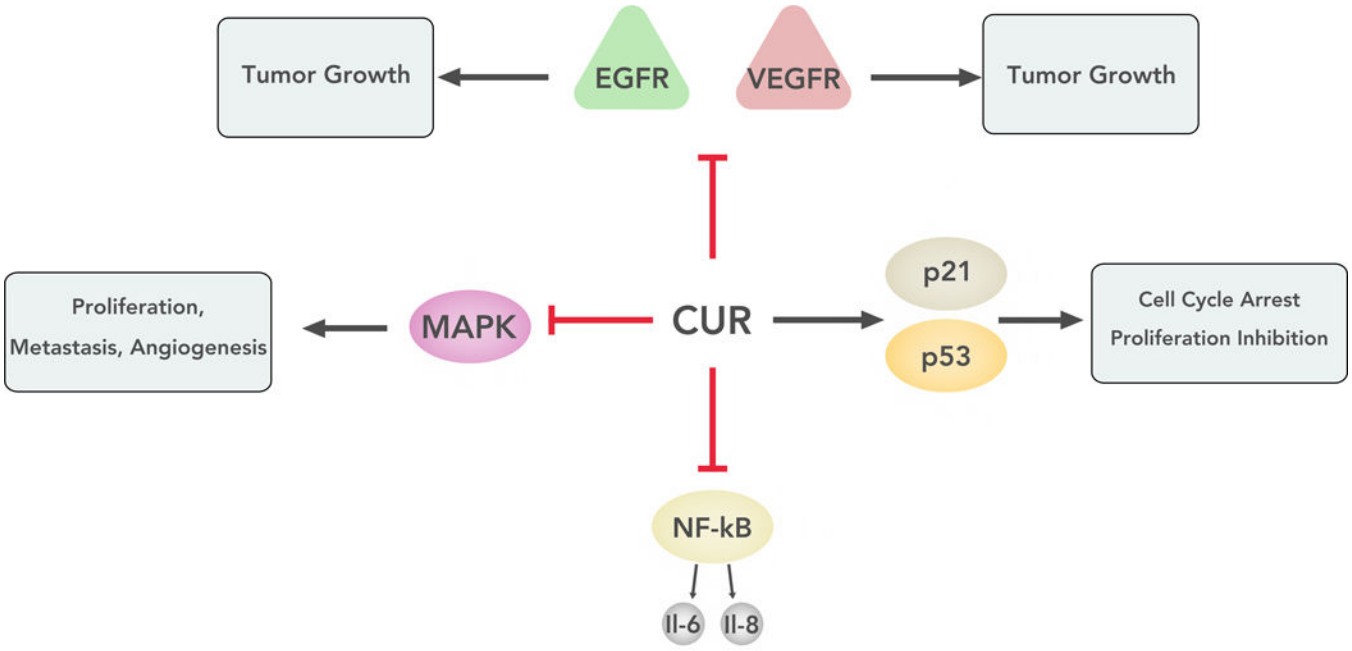

Figure 2.

The figure shows the various signaling pathways affected by curcumin. The molecule can act to inhibit a number of pathways that allow for tumor growth and invasion. Curcumin can also lead to upregulation of molecules that lead to cell cycle arrest in tumor cells. EGFR = epidermal growth factor receptor; VEGFR = receptors for vascular endothelial growth factors; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK = mitogen-activated protein kinases; p53 = tumor protein p53; p21 = cyclin-dependent kinase inhibitor 1

TABLE 1

Important Natural Forms and Derivatives of Chemopreventive Natural Compounds in HNSCC

Natural Compound	Important Natural Forms and Derivatives	
	Name	Source
Vitamin A	Retinyl palmitate, isoretinoin, β-carotene	(6–9,12,13,98)
Isothiocyanate	PEITC, BITC, sulforaphane	(28,31,36)
Green Tea	EC, EGC, ECG, EGCG	(2,38,40,49)

TABLE 2

The Most Promising Studies of Chemopreventive Natural Compounds in HNSCC

	Most Promising Trials			
Natural Compound	**Type**	**Compound**	**Result**	**Source**
Vitamin A	Clinical	Isoretinoin, interferon-α, α-tocopherol	Improved survival rate and lowered secondary primary tumors	(6,12,13)
Curcumin	Clinical	Curcumin	Reduced oral premalignant and high risk lesions	(23,24)
Isothiocyanate	Pre-clinical	BITC, cisplatin	Increase in apoptosis and decrease in HNSCC cell viability	(31,32)
Green Tea	Clinical	GTE, erlotinib	Reduced oral premalignant lesions	(47)
Luteolin	Pre-clinical	EGCG, luteolin	Induced apoptosis, inhibited growth of xenograft tumors	(58)
Resveratrol	Pre-clinical	Resveratrol	Induced apoptosis	(99)
Genistein	Pre-clinical	Cetuximab, genistein	Tumor growth inhibition, apoptosis	(83)
Lycopene	Clinical	Lycopene	Reduction in HNSCC	(92)
Bitter Melon	Pre-clinical	BME	Inhibition of HNSCC growth in mice	(93,95)
Withaferin A	Pre-clinical	Withaferin A	Apoptosis of HNSCC cell lines	(96)
Guggulsterone	Pre-clinical	Guggulsterone	Increased efficacy of erlotinib, cetuximab and cisplatin	(97)

BITC = benzyl isothiocyanate, GTE = green tea extract, EGCG = epigallocatechin-3-gallate, BME = 2-Mercaptoethanol

TABLE 3

Current Obstacles and Solutions for Chemopreventive Natural Compounds in HNSCC

Natural Compound	Obstacles	Current Solutions	Source
Vitamin A	toxicity	In combination, analogs, bioadjuvant	(6–8,11–13)
Curcumin	bioavailability	analogs, bioadjuvant, liposomal, nanoparticles, phospholipid complex, in combination	(4,5,15–17,21,23)
Isothiocyanate	lack of studies specific to HNSCC	In combination, analogs	(37)
Green Tea	bioavailability	In combination, analogs	(1,47,49)
Luteolin	bioavailability, lack of studies specific to HNSCC	Nanoparticles, in combination	(100)
Resveratrol	bioavailability, lack of studies specific to HNSCC	Nanoparticles, in combination, bioadjuvant	(61,70–72)
Genistein	lack of studies specific to HNSCC	In combination	(3,83)
Lycopene	lack of studies specific to HNSCC	In combination, bioadjuvant	(3,84)
Bitter Melon	lack of studies specific to HNSCC	Early stages of investigation	(93–95)
Withaferin A	lack of studies specific to HNSCC	Early stages of investigation	(96)
Guggulsterone	lack of studies specific to HNSCC	Early stages of investigation	(97)