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The Potential Use of Glucosinolates in Oral Cancer Therapy: A Comprehensive Review

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ABSTRACT

Oral cancer is a significant global health burden, and current treatment modalities often entail side effects and limited efficacy. Hence, there is a growing interest in exploring natural compounds with potential anticancer properties as alternative or complementary therapies. Glucosinolates, found abundantly in cruciferous vegetables, have shown promising bioactive metabolites with demonstrated anticancer effects in various malignancies. This comprehensive review aims to explore the potential use of glucosinolates in oral cancer therapy, synthesizing existing evidence from in vitro studies and clinical trials.

The review looks into the mechanisms of action underlying the potential anticancer properties of glucosinolates and their metabolites. Isothiocyanates, the major bioactive derivatives of glucosinolates, have been found to induce apoptosis, cell cycle arrest, and inhibit tumour growth in oral cancer cell lines and animal models. The modulation of key signalling pathways and the inhibition of angiogenesis and metastasis by glucosinolates, have been reported. Moreover, in vitro studies have highlighted the synergistic effects of glucosinolates with conventional chemotherapeutic agents, providing a basis for combination therapies.

The comprehensive review presents a compelling body of evidence supporting the potential use of glucosinolates in oral cancer therapy. The growing interest in natural compounds as therapeutic agents, glucosinolates hold promise as a valuable addition to the collection of oral cancer treatment options. However, further research, including well-designed clinical trials, is needed to establish their safety, efficacy, and optimal dosages in the clinical setting.

Keywords– Glucosinolates, Oral Cancer, Phenethyl isothiocyanate, Cruciferous vegetables

1. INTRODUCTION

1.1 Oral Cancer overview

Oral cancer is a malignant neoplasia which arises on the lip or oral cavity. Oral cancer is two to three times more prevalent in men than women in most ethnic groups. [1] It is a type of head and neck cancer and can have serious health implications if not diagnosed and treated in its early stages. Carcinoma most commonly arose from radicular cyst (60%) followed by dentigerous cyst (16%), keratocystic odontogenic tumor (odontogenic keratocyst) (14%) and lateral periodontal cyst (1%). [2]

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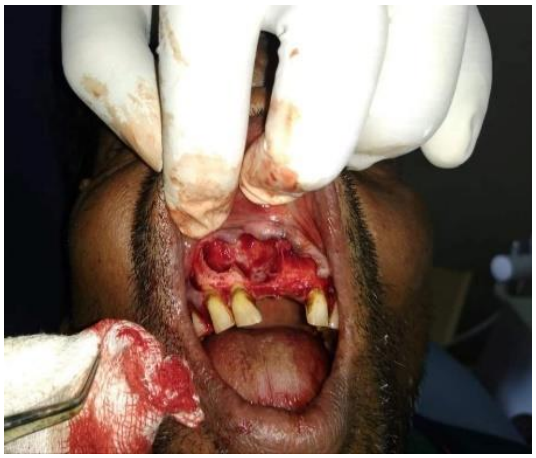

Figure – 1: - Radicular Cyst

1.2 Limitations of Current Therapies

Current therapies for oral cancer have several limitations, which can impact their effectiveness and overall outcomes for patients. Some of the key limitations include:

1. Late-stage diagnosis: One of the major limitations is that oral cancer is often diagnosed at an advanced stage when the tumor has already grown or metastasized to other parts of the body. Late-stage diagnosis reduces the effectiveness of treatments and leads to lower survival rates.

2. Surgical challenges: Surgery is a common treatment for oral cancer, but it can be challenging due to the complex anatomy and delicate structures involved. Complete removal of the tumour while preserving normal tissue and function can be difficult, leading to potential complications and functional impairments.

3. Radiation therapy side effects: Radiation therapy is commonly used in combination with surgery for oral cancer. While it can effectively target and kill cancer cells, it also affects surrounding healthy tissues, leading to side effects such as mucositis, xerostomia (dry mouth), difficulty swallowing, and dental problems.

4. Chemotherapy limitations: Chemotherapy is often used in advanced or metastatic oral cancer cases. However, its efficacy can be limited due to the resistance of cancer cells to certain drugs. Moreover, chemotherapy drugs can cause significant side effects, including nausea, hair loss, fatigue, and immuno-suppression.

5. Psychological and functional impact: Oral cancer and its treatments can have significant psychological and functional impacts on patients. The loss of oral function, changes in appearance, difficulties in speech, eating, and swallowing, as well as the emotional stress associated with the disease, can significantly affect the quality of life for the patient.

2. Glucosinolates and Their Bioactive Metabolites

2.1 Definition and sources of Glucosinolates

Glucosinolates are a group of natural compounds found in cruciferous vegetables, which are part of the Brassicaceae family. They are sulphur-containing compounds that are responsible for the characteristic taste and aroma of these vegetables. Glucosinolates act as a defence mechanism for the plants against pests and pathogens. [3]

Cruciferous vegetables rich in glucosinolates include:

- Broccoli: Broccoli is a popular vegetable that contains various types of glucosinolates, including glucoraphanin, gluconasturtiin, and glucobrassicin.
- Brussels Sprouts: Brussels sprouts are small, leafy green vegetables that are high in glucosinolates, particularly sinigrin.
- Cauliflower: Cauliflower is a versatile vegetable that contains glucosinolates such as glucoraphanin and glucobrassicin.

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- Cabbage: Cabbage, including green cabbage, red cabbage, and Savoy cabbage, contains glucosinolates such as glucoraphanin, sinigrin, and gluconasturtiin.
- Kale: Kale is a nutrient-dense leafy green vegetable that contains various glucosinolates, including glucoraphanin and glucobrassicin.
- Radishes: Radishes, including daikon radish and red radish, are root vegetables rich in glucosinolates like glucoraphanin and glucobrassicin.
- Watercress: Watercress is a leafy green vegetable with a peppery flavor and high glucosinolate content, primarily gluconasturtiin.

Other cruciferous vegetables, such as arugula, mustard greens, turnips, and horseradish, also contain varying amounts of glucosinolates.

It is important to note that the specific types and concentrations of glucosinolates may vary among different vegetables and even within different cultivars of the same vegetable. Additionally, the cooking process, such as boiling or microwaving, can affect the glucosinolate content in these vegetables. [4]

Consuming a variety of cruciferous vegetables can provide a natural dietary source of glucosinolates, which have been associated with several therapeutic benefits, including potential anti-cancer properties. [5]

2.2 Activation and conversion of Glucosinolates to bioactive metabolites

Glucosinolates are relatively stable compounds that undergo enzymatic hydrolysis to yield various bioactive metabolites. The conversion of glucosinolates into bioactive compounds occurs through a process known as hydrolysis, which can be initiated by endogenous enzymes or microbial enzymes.

1. Myrosinase-Mediated Hydrolysis: The primary pathway for glucosinolate hydrolysis involves the enzymatic action of myrosinase. Myrosinase is an endogenous enzyme found in cruciferous vegetables that catalyzes the hydrolysis of glucosinolates into several bioactive metabolites. This process typically occurs when plant tissues are damaged, such as through chopping, chewing, or processing. The steps involved in myrosinase-mediated hydrolysis are as follows:

   a. Glucosinolate breakdown: Myrosinase cleaves the β-glucosidic bond of the glucosinolate molecule, releasing glucose and an unstable aglycone intermediate known as a thiohydroximate-O-sulfonate.

   b. Formation of isothiocyanates: The thiohydroximate-O-sulfonate can undergo spontaneous rearrangement, known as the epithionitrile pathway, or react with water to form an isothiocyanate. Isothiocyanates are the most common class of bioactive metabolites derived from glucosinolates and are known for their potential chemopreventive and anticancer activities.

   c. Formation of other metabolites: In some cases, the aglycone intermediate can undergo further transformations, leading to the formation of other bioactive compounds, such as nitriles or thiocyanates, depending on the specific glucosinolate and reaction conditions. [6]

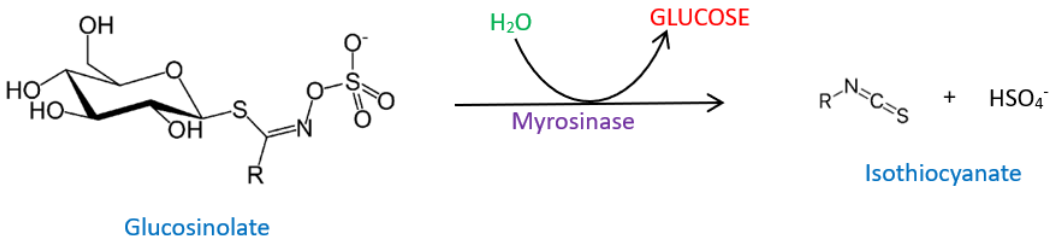

Figure - 2: Hydrolysis of Glucosinolate by Myrosinase and Formation of Isothiocyanate (ITC).[7]

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2. Gut Microbiota-Mediated Hydrolysis:
Glucosinolates that escape myrosinase hydrolysis in the upper digestive tract can reach the large intestine, where they can be metabolized by the gut microbiota. Certain bacteria in the gut possess specialized enzymes, such as sulfatases and β-glucosidases, which can hydrolyze glucosinolates and convert them into bioactive metabolites. The gut microbiota-mediated hydrolysis can lead to the formation of various metabolites, including isothiocyanates, indoles, and organic acids, depending on the specific gut microbial composition and enzymatic activities. [8]

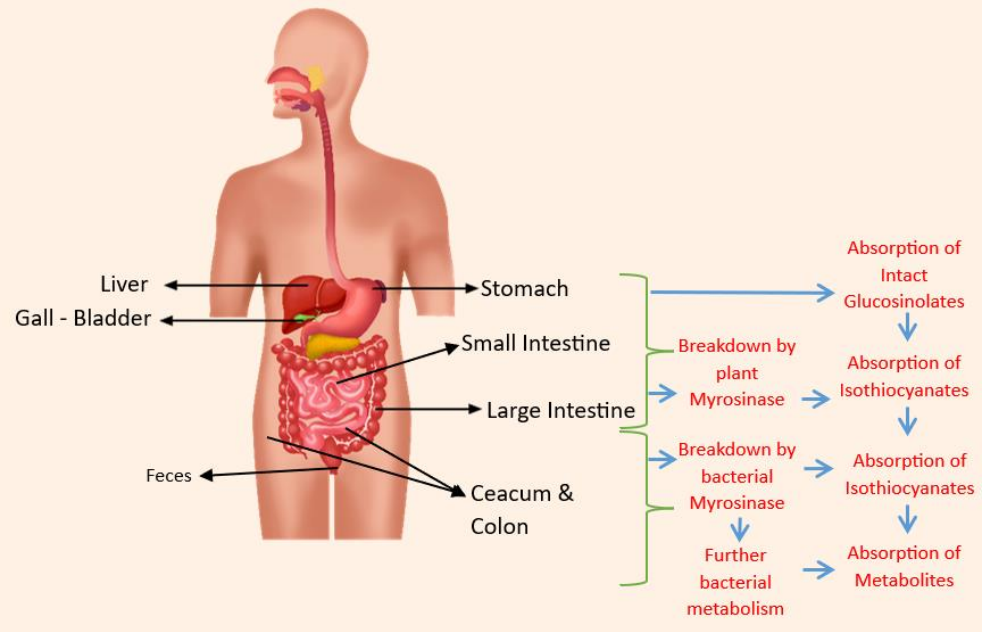

Figure – 3: Summary of the fate of Glucosinolates and their breakdown products in the Human gut. [9]

2.3 Major bioactive metabolites and their potential mechanisms of action

The bioactive metabolites derived from glucosinolates, particularly isothiocyanates, have been extensively studied for their potential health benefits, including their chemopreventive, anticancer, anti-inflammatory, and antioxidant properties. However, it is crucial to consider the stability, bioavailability, and metabolism of these metabolites when assessing their potential therapeutic effects.

Some of the commonly studied and well-known isothiocyanates derived from specific glucosinolates include:

I. Sulforaphane: Derived from glucoraphanin, which is found in high concentrations in broccoli and broccoli sprouts. Sulforaphane has shown potent anticancer, anti-inflammatory, and antioxidant activities. It is considered one of the most extensively studied and promising isothiocyanates.
II. Phenethyl isothiocyanate (PEITC): Derived from gluconasturtiin, which is present in cruciferous vegetables like watercress and garden cress. PEITC exhibits anticancer effects by inducing cell cycle arrest and apoptosis in various cancer cell lines.
III. Benzyl isothiocyanate (BITC): Derived from glucotropaeolin, which is found in vegetables like garden cress and watercress. BITC has demonstrated anticancer properties by inhibiting tumor growth and metastasis and inducing apoptosis.
IV. Allyl isothiocyanate (AITC): Derived from sinigrin, which is found in high amounts in mustard seeds and wasabi. AITC has exhibited antimicrobial, antioxidant, and anti-inflammatory activities.

Regulation of Apoptosis by PEITC

Among the isothiocyanates available from dietary sources, PEITC is an aromatic isothiocyanates that has been extensively studied for its chemopreventive potential [10]. PEITC is known to induce NADPH quinine reductase and glutathione Stransferase (GST) (phase II detoxification enzymes), to inhibit several P450 enzymes that are involved in metabolic activation of carcinogens, and to sensitize the cells to apoptosis by sustained activation of JNK and stress-activated protein kinase pathway [11] [12] [13]. Recent studies have indicated

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that PEITC induces apoptosis in cancer cells [14]. PEITC-induced apoptosis was shown to be associated with a rapid and transient induction of caspase-3-like activity, activation of JNK, and involvement of p53 [13] [14] [15]. Here is some key ways in which PEITC induces apoptosis:

- Activation of Caspases: PEITC activates caspases, which are key enzymes involved in apoptosis. Caspases are proteases that cleave specific proteins and initiate the dismantling of cellular components during apoptosis. PEITC activates caspase-9, the initiator caspase, by releasing it from its inhibitory protein (e.g., apoptosis protease-activating factor-1, Apaf-1). Activated caspase-9 then activates downstream executioner caspases, such as caspase-3 and caspase-7, leading to the cleavage of various cellular substrates and execution of apoptosis.
- Mitochondrial Dysfunction: PEITC targets the mitochondria, which play a critical role in regulating apoptosis. It causes mitochondrial membrane depolarization, leading to the release of pro-apoptotic proteins, such as cytochrome c, from the mitochondria into the cytosol. Once released, cytochrome c forms a complex with Apaf-1 and caspase-9, forming the apoptosome complex that activates caspase-9 and triggers the downstream apoptotic cascade.
- Bcl-2 Family Protein Modulation: The Bcl-2 family of proteins regulates mitochondrial apoptosis by controlling the permeability of the mitochondrial outer membrane. PEITC can modulate the balance between pro-apoptotic (e.g., Bax, Bak) and anti-apoptotic (e.g., Bcl-2, Bcl-xL) members of the Bcl-2 family. PEITC increases the expression of pro-apoptotic proteins and reduces the levels of anti-apoptotic proteins, resulting in mitochondrial outer membrane permeabilization and subsequent apoptosis.
- p53 Activation: PEITC can activate the tumor suppressor protein p53, which plays a crucial role in regulating cell cycle arrest and apoptosis. Activated p53 induces the expression of pro-apoptotic proteins, such as Bax and PUMA, and represses the expression of anti-apoptotic proteins, such as Bcl-2 and survivin. This leads to mitochondrial dysfunction and caspase activation, ultimately promoting apoptosis.
- ROS Generation: PEITC can increase the generation of reactive oxygen species (ROS) within cancer cells. Excessive ROS accumulation can cause oxidative stress and trigger apoptotic pathways. PEITC-induced ROS production can disrupt mitochondrial function, activate caspases, and initiate apoptosis.

Regulation of cell cycle arrest by PEITC

The cell cycle consists of a regulated series of stages involving growth and division, resulting in the formation of two daughter cells. Various checkpoints monitor signals for growth, nutrient availability, and DNA integrity. Phenethyl isothiocyanate (PEITC) has been shown to influence cell cycle progression and regulate cell proliferation, making it a potential target for anti-cancer therapies. The inhibition of cell cycle progression and proliferation by PEITC primarily occurs by targeting key proteins involved in cell cycle progression and the expression of cyclin-dependent kinase (CDK) inhibitors (**Traka and Mithen, 2009**). The cell cycle consists of distinct phases, including G1 (before DNA replication) and G2 (from DNA replication to mitosis), regulated by cyclins and cyclin-dependent kinases (CDKs). These protein kinases serve as the signal that regulate G1 and G2 checkpoints for the transition from G1 phase to S phase and from G2 phase to M phase (**Singhal et al., 2015**). There was evidence indicating the mechanistic basis behind glucosinolates derived isothiocyanates associated with cell cycle arrest at various phases of cell cycle depending on the cell type used in the study. Consistent with these, (**Hasegawa et al., 1993**) was the first to report the potency of isothiocyanates in modulating the cell cycle progression. PEITC treatment has been found to induce cell cycle arrest at different phases depending on the cell type studied. For instance, it has been reported to cause G2/M phase arrest and inhibit cell growth in HeLa cells. In Caco-2 colon cells, PEITC induced the expression of the CDK inhibitor p21waf1/cip1, leading to G2 phase arrest, (**Visanji et al., 2004)**. PEITC's mechanism of action involves covalently binding to cysteine residues in tubulin, disrupting microtubule formation and function, leading to G2/M phase arrest and apoptosis (**Mi et al., 2009**). It was interesting that PEITC down regulated the protein levels of cyclin-dependent kinase 1 (Cdk1) and Cdc25C in a dose dependent manner causing G2/M phase arrest and apoptosis in PC-3 prostate cells (**Xiao et al., 2004**). Notably, even subtle structural changes, as seen with the similar compound PITC, can affect the efficacy of biological activity (**Xiao et al., 2004)**. The potential protective mechanisms and effects of PEITC leading to cell death are summarized in Table 1. [16]

Table – 1: Summary of Potential Action Mechanism of PEITC in Relation to Its Apoptosis-inducing Ability against various Cell Lines. [17]

Action mechanism	Cell lines/ animal model	References

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a. Cell cycle arrest		
G0/G1arrest and increase of p21 protein	DU-14 cells, Human prostate cancer	Chiao et al., 2000
G0/G1arrest and increase of p21 protein	LNCaP cells, Human prostate cancer	Chiao et al., 2000
G2/M phase arrest and decrease in Bcl-2 and, Bcl-X(L)	PC-3 cells, Human prostate cancer	
G2/M phase arrest	Hela cells	Hasegawa et al., 1993
G2phase arrest, induction of CDK inhibitor p21waf1/cip1	Caco-2 cells, human colon cancer	Visanji et al., 2004
G2/M phase arrest	PC-3, Human prostate cancer	Xiao et al., 2004
b. Oxidative stress		
Depletion of glutathione (GSH)	Ovarian epithelial cells	Trachootham et al., 2006
c. Induction of apoptosis		
Induced p53 independent apoptotic pathway	PC-3 cells, Human prostate cancer	Xiao and Singh, 2002
Action mechanism	**Cell lines/ animal model**	**References**
Activation of JNK, ERK and p38	HT-29, human colon cells	Hu et al., 2003
Activation of JNK	Various of cell lines	Chen et al., 1998; 2002
ROS mediated apoptosis	PC-3 cells, Human prostate cancer	Xiao et al., 2006
Inhibition of angiogenesis	HUVEC, human umbilical vein endothelial cells	Xu et al., 2005

3. Anticancer Effects of Glucosinolates in Oral Cancer

3.1 In vitro studies demonstrating anticancer properties

- While several studies have been conducted to investigate the impact of isothiocyanates on cancer risk and growth[18], no prior research has explored the potential benefits of isothiocyanates in treating ovarian carcinoma. Therefore, this present study aimed to assess the therapeutic potential of PEITC (phenethyl isothiocyanate) in ovarian cancer. We specifically examined the antiproliferative and apoptotic effects of PEITC in OVCAR-3 ovarian cancer cells. Additionally, we investigated the role of caspases and the underlying signaling pathways involved in the mechanism of action of PEITC on OVCAR-3 cells.
- The growth-inhibitory effect of PEITC on various gynecologic cancer cells was evaluated using a panel of seven different cell lines representing different gynecologic malignancies, including ovarian cancer (SKOV-3, NUTU-19, and OVCAR-3), vulvar cancer (SW954), cervical cancer (HeLa and SW756), and endometrial cancer (KLE) [19]. The cells were treated with increasing concentrations of PEITC (ranging from 0 to 100 μM) for 48 hours, and the IC50 values, representing the concentration required for a 50% reduction in cell viability compared to untreated controls, were determined to assess the effectiveness of PEITC. The results revealed a significant inhibition of growth in all the tested gynecologic cancer cells.
- Numerous studies have shown that isothiocyanates (ITCs) trigger apoptosis in cultured cells, leading to characteristic DNA ladders. For example, **Gamet-Payrastre et al.** demonstrated that sulforaphane (SFO) induced apoptosis in HT29 human colon cancer cells. Similarly, **Yu et al.** observed that treatment with 10 μM of benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), phenyl isobutyl isothiocyanate (PBITC), or phenylhexyl isothiocyanate (PHITC) for 8 hours caused HeLa cells to display condensed and fragmented nuclei, which are typical hallmarks of apoptotic cell death, as visualized using the fluorescent DNA-binding agent, DAPI.
- **Huang et al.** found that in mouse epidermal JB6 cells, the initiation of apoptosis through PEITC takes place via a pathway dependent on the presence of p53.[20]
- The findings revealed that PEITC induced an increase in p53 expression in a manner dependent on both the dosage and duration of exposure, leading to p53-dependent transcriptional activation. Apoptosis triggered by PEITC was observed in p53 +/+ cells, but not in p53 -/- cells, indicating that elevated levels of p53 were essential for the induction of apoptosis by PEITC in JB6 cells.[20]

3.2 Molecular mechanisms underlying the anticancer effects

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Phenethyl Isothiocyanate

Though phenethyl isothiocyanate (PEITC) is found across crucifers, it is highly abundant in water cress [21]. Precursor of PEITC is gluconasturtiin. It has a higher potential to induce ROS and oxidative damage to cancer cells.

Blood

PEITC reduced the growth of blood tumor cell by inducing Fas and Fas ligand (FasL) expression and ROS generation [22]. Fas is a member of the death receptor family (type I membrane protein) and FasL is type II transmembrane protein, belongs to TNF family. Fas-FasL binding plays a fundamental role in apoptosis [23]. This interaction triggers the programmed cell death as an immune response. Subsequent release of cytochrome c and stimulation of caspase-3 and -9 caused the cell death [22]. Chronic lymphocytic leukemia (CLL), affects mainly the adult and it is also resistant to fludarabine (chemotherapy medicine used to treat leukemia and lymphoma). Exposure of both resistant and sensitive CLL cell lines to PEITC leads to massive cell death due to the glutathione depletion, higher ROS generation and oxidation of mitochondrial cardiolipin [24].

Colon

Similar to BITC, PEITC also possesses antimetastatic property. Invasion and migration of colon cancer was prevented by the inhibition of genes involved in the cell cycle such as the son of sevenless homolog 1 (SOS-1), PKC, ERK1/2 and Ras homolog gene family, member A (Rho A). SOS is critical for cell growth and differentiation. RhoA associated with the cytoskeleton regulation directly alter the cell signaling proteins for inflammation or cell growth, MMP-2, MMP-9, Ras, focal adhesion kinase (FAK), PI3K, growth factor receptor-bound protein 2 (GRB2), NF-κB, inducible isoform of nitric oxide synthases (iNOS), COX-2, AKT and JNK [25]. Inflammation of colon cancer was reduced under PEITC treatment. Induction of mitochondria caspase cascade and JNK, critical factors for the initiation of apoptotic was observed in PEITC treated HT-29, colon cancer cell [26]. Anti-inflammatory effect of PEITC against colon cancer was correlated with the lesser expression of NF-κB [27].

Breast

The reduction of human epidermal growth factor receptor 2 (HER2) and STAT3 promotes the activation of caspase-3 and poly (ADP-ribose) polymerase (PARP) in breast cancer cell lines [28]. HER2, a member of the epidermal growth factor receptor (EGFR) family, is commonly overexpressed in various cancer types. HER2 plays a role in regulating cell growth, survival, and differentiation, and decreasing its expression can help control excessive cell growth [29]. Isothiocyanates (ITCs) stimulate DNA fragmentation and cleavage of PARP, which is involved in DNA repair, genomic stability, and programmed cell death. PARP is activated under cellular stress conditions, and its hyperactivation leads to ATP depletion during the repair of damaged DNA, ultimately resulting in cell death [30]. The apoptotic process is associated with increased expression of caspase-3 and -9, followed by the generation of reactive oxygen species (ROS) [31]. Targeting the hyperactivation of PARP, which causes NAD+/ATP depletion, is a potential strategy for cancer therapy [30]. Combining PEITC with taxol, a commercial drug, effectively inhibits breast cancer cell lines compared to individual treatments. This combination leads to the prevention of cell proliferation by reducing the expression of cyclin-dependent kinase 1 (cdk1), a cell cycle regulator, and B-cell lymphoma 2 (bcl 2), an anti-apoptotic protein [32].

Ovary

PEITC treatment resulted in a reduced phosphorylation rate of the EGFR/AKT pathway in ovarian tumor cells. Blocking EGFR and HER2, which are upstream regulators of Akt, prevents cancer cell proliferation. In prostate cancer, blocking HDAC inhibits the androgen receptor. HDAC is associated with processes such as cell proliferation, cell cycle regulation, and apoptosis, which are linked to tumor development. PEITC inhibited oncogenic pathways including EGFR, HER2, and Akt [33]. Additionally, PEITC decreased the expression of chromosomal maintenance 1 (CRM1) proteins [34]. CRM1 is involved in centrosome duplication and spindle assembly and facilitates the transport of large macromolecules across the membrane. Treatment with metformin and PEITC sensitized cisplatin-resistant ovarian cancer cells, leading to increased sensitivity to the drug. Higher levels of reactive oxygen species (ROS) impeded the growth of ovarian cancer cells and ultimately induced cell death [35]. The metabolic pathways involved in cancer prevention by PEITC are illustrated in Figure 7.

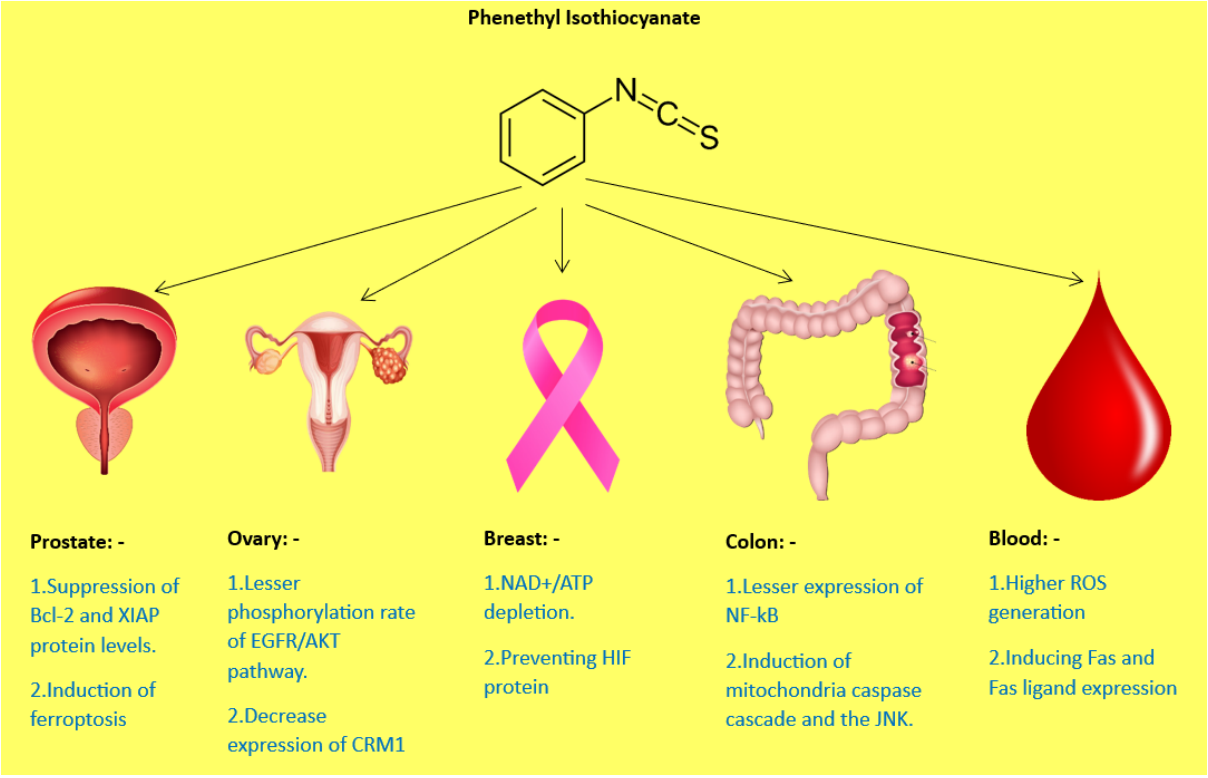

Figure – 4: - Important metabolic pathways involved by phenethyl isothiocyanate (PEITC) in the prevention of cancers. [36]

4. Clinical Evidence and Translational Potential

4.1 Clinical studies investigating glucosinolate-derived compounds

Clinical studies investigating glucosinolate-derived compounds in oral cancer are limited, here are a few relevant studies:

- A randomized clinical trial examined the effect of a broccoli sprout extract rich in glucosinolates on the oral mucosa of patients at high risk of oral cancer. The results showed that the extract significantly increased the expression of genes involved in detoxification and antioxidant pathways in the oral mucosa.
- Another clinical trial evaluated the effects of broccoli sprout extract on oral leukoplakia, a potentially malignant oral lesion. The researchers found that the extract significantly increased the expression of genes associated with detoxification and protection against oxidative stress, suggesting a potential chemopreventive effect.
- A study investigated the chemopreventive effects of broccoli sprout extract in individuals with oral squamous cell carcinoma (OSCC), the most common type of oral cancer. The results indicated that the extract modulated several biomarkers related to oxidative stress, inflammation, and cell proliferation, suggesting a potential role in OSCC prevention.
- A clinical trial examined the effect of a combination of broccoli sprout extract and curcumin (a compound found in turmeric) on oral potentially malignant disorders. The results suggested that the combination treatment reduced the severity of oral lesions and improved clinical outcomes.

4.2. Future directions for research and clinical applications

The field of glucosinolate research holds significant promise, and several future directions can be pursued to advance our understanding and clinical applications of these bioactive compounds. Here are some potential future directions for research and clinical applications of glucosinolates:

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- Identification and Characterization of Novel Glucosinolate Derivatives**:** While the anticancer properties of certain glucosinolates have been extensively studied, there is a need to explore other glucosinolate derivatives and their potential biological activities. Identifying and characterizing novel glucosinolate derivatives may uncover compounds with enhanced efficacy or novel mechanisms of action, expanding the therapeutic options for cancer treatment.
- Development of Targeted Delivery Systems**:** Enhancing the bioavailability and targeted delivery of glucosinolates to cancer cells is crucial for their clinical application. Future research can focus on developing innovative delivery systems, such as nanoparticles or liposomes, that can improve the stability, solubility, and targeted delivery of glucosinolates to tumor tissues while minimizing off-target effects.
- Combination Therapies**:** Investigating the potential synergistic effects of glucosinolates with conventional cancer therapies is an important area for future research. Combination therapies involving glucosinolates and chemotherapy drugs, radiation therapy, or immunotherapies can be explored to improve treatment outcomes, reduce drug resistance, and minimize side effects.
- Personalized Medicine Approaches**:** Considering the inter-individual variability in response to glucosinolates, personalized medicine approaches can be explored to optimize treatment outcomes. Identifying biomarkers or genetic profiles that predict individual responses to glucosinolates can help tailor treatment strategies and optimize dosage regimens for maximum efficacy.
- Clinical Trials and Translational Research: Conducting well-designed clinical trials to evaluate the safety, efficacy, and optimal dosages of glucosinolates in cancer patients is essential for their clinical translation. Large-scale clinical trials can provide valuable insights into the therapeutic potential of glucosinolates and their effectiveness in specific cancer types.
- Mechanistic Studies**:** Further investigations into the molecular mechanisms underlying the anticancer effects of glucosinolates can enhance our understanding of their mode of action. Elucidating the precise molecular targets, signalling pathways and interactions with cellular components will provide a foundation for the development of targeted therapies and the identification of predictive biomarkers.
- Beyond Cancer**:** Exploring the potential applications of glucosinolates beyond cancer therapy is an exciting avenue for future research. Glucosinolates have been implicated in various other health benefits, such as cardiovascular health, neuroprotection, and anti-inflammatory effects. Investigating their potential in these areas can broaden their therapeutic applications.

5. Safety and Potential Side Effects

5.1 Evaluation of glucosinolate safety profiles

It is important to evaluate the safety profiles of glucosinolates, particularly in relation to oral cancer.

1. Toxicity: Glucosinolates can be hydrolyzed into various breakdown products, including isothiocyanates (ITCs), which have shown anti-cancer activity. However, high doses of ITCs can be toxic and may cause adverse effects such as gastrointestinal disturbances and skin irritation. The toxicity of glucosinolates and their breakdown products largely depends on the dose and duration of exposure.
2. Oral Cavity Effects: As oral cancer primarily affects the tissues in the mouth, it is essential to assess the potential effects of glucosinolates on the oral cavity. Some studies have suggested that glucosinolates and ITCs may have anti-cancer effects on oral cancer cells. However, more research is needed to determine their effectiveness, optimal dosages, and potential side effects in the oral cavity.
3. Drug Interactions: Glucosinolates and ITCs can potentially interact with certain medications. For example, ITCs can inhibit cytochrome P450 enzymes, which are responsible for metabolizing many drugs. This interaction may alter the efficacy and safety of certain medications, and individuals taking medications should exercise caution when consuming high doses of glucosinolate-rich foods or supplements.
4. Individual Variability: People may have different tolerances and sensitivities to glucosinolates and their breakdown products. Genetic variations in enzymes involved in glucosinolate metabolism can affect an individual's response to these compounds. Factors such as age, underlying health conditions, and overall diet can also influence the safety and effectiveness of glucosinolates in oral cancer prevention or treatment.

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5. Comprehensive Approach: It is important to consider glucosinolates as part of an overall dietary approach to reduce the risk of oral cancer. Consuming a diverse range of fruits and vegetables, including cruciferous vegetables, along with a balanced diet, can provide various beneficial compounds that work synergistically to promote health and reduce the risk of cancer.

5.2 Potential side effects and toxicity concerns

Potential side effects and toxicity concerns of glucosinolates in oral cancer therapy are:

1. Isothiocyanates: Glucosinolates are converted into isothiocyanates (ITCs) when the vegetables are chewed, chopped, or otherwise processed. ITCs have been studied for their anticancer effects, including oral cancer. However, high doses of ITCs may have toxic effects and can cause irritation, allergic reactions, and gastrointestinal disturbances. It's worth noting that these effects are primarily associated with high dietary intake of ITC-rich foods, rather than the use of isolated ITC compounds as oral cancer therapy.
2. Drug interactions: Glucosinolates and ITCs can interact with certain medications. They may induce or inhibit drug-metabolizing enzymes in the liver, which can alter the metabolism and effectiveness of medications. If a person undergoing oral cancer therapy is taking other medications, it's important to consult with a healthcare professional to assess potential interactions.
3. Individual sensitivities: Some individuals may be more sensitive to the effects of glucosinolates or ITCs. Allergic reactions, skin rashes, or gastrointestinal discomfort may occur in susceptible individuals.
4. Goitrogenic effects: Glucosinolates can interfere with iodine uptake by the thyroid gland, potentially affecting thyroid function. However, the goitrogenic effects are primarily observed with very high intake of raw cruciferous vegetables.

5.3 Strategies to enhance safety and minimize adverse effects

It's important to consider safety and minimize adverse effects when incorporating glucosinolates into oral cancer therapy. Here are some strategies to enhance safety:

1. Optimal dosage: Excessive intake of glucosinolates may lead to adverse effects, so it's important to follow the recommended dosage guidelines.
2. Choose the right food sources: Cruciferous vegetables are the primary dietary source of glucosinolates. However, some people may be more sensitive to these compounds than others. If you have a high sensitivity to glucosinolates or experience adverse effects, you can consider alternative sources, such as supplements or processed foods with controlled glucosinolate content.
3. Food preparation techniques: The bioavailability of glucosinolates can vary based on the cooking methods used. To minimize adverse effects, consider lightly steaming or stir-frying cruciferous vegetables, as excessive cooking or overprocessing may reduce the beneficial compounds or cause degradation.
4. Monitoring and adjusting intake: Keep track of your glucosinolate intake and monitor any adverse effects; it may be necessary to adjust the intake or temporarily stop using glucosinolate-rich foods or supplements.
5. Consider individual tolerances: Individuals may vary in their ability to metabolize and tolerate glucosinolates. Some people may experience digestive issues, such as bloating or gas, while others may not.
6. Balanced diet: While glucosinolates may have potential anticancer properties, it's important to maintain a balanced diet and include a variety of other nutrient-rich foods. A well-rounded diet with a variety of fruits, vegetables, whole grains, lean proteins, and healthy fats can provide essential nutrients and support overall health during oral cancer therapy.

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6. Combination Therapies and Synergistic Effects

6.1 Synergy with conventional treatments

It may potentially synergize with conventional treatments for oral cancer:

1. Chemo-preventive effects: Glucosinolates have been shown to have chemopreventive properties, meaning they may help prevent the development and progression of cancer. Some studies have found that glucosinolates can inhibit the growth of cancer cells and induce apoptosis (programmed cell death) in oral cancer cells. When used in combination with conventional treatments such as surgery, radiation, or chemotherapy, glucosinolates may enhance their effectiveness.
2. Enhanced treatment response: Research suggests that glucosinolates can sensitize cancer cells to conventional treatments. They may enhance the efficacy of chemotherapy drugs or radiation therapy by increasing cancer cell sensitivity to these treatments. This could potentially lead to better treatment outcomes for oral cancer patients.
3. Reduced side effects: Conventional treatments for oral cancer, such as chemotherapy and radiation therapy, can cause significant side effects. Glucosinolates have been investigated for their potential to reduce the side effects of these treatments. For example, some studies have suggested that glucosinolates may help protect healthy cells from the toxic effects of chemotherapy or radiation, thereby minimizing the side effects experienced by patients.
4. Anti-inflammatory effects: Chronic inflammation has been linked to the development and progression of cancer. Glucosinolates have anti-inflammatory properties and may help reduce inflammation in the oral cavity.

6.2 Combinatorial approaches to enhance therapeutic outcomes

Combinatorial approaches involving glucosinolates have been explored to enhance therapeutic outcomes in oral cancer. Here are a few strategies that have been studied:

1. Combination with chemotherapy: Glucosinolates have been investigated as potential adjuncts to conventional chemotherapy drugs used in oral cancer treatment. Studies have shown that combining glucosinolates with chemotherapeutic agents can enhance the efficacy of the drugs, reduce drug resistance, and minimize adverse effects. For example, a combination of glucosinolates and cisplatin, a commonly used chemotherapy drug, has demonstrated synergistic effects in inhibiting oral cancer cell growth.
2. Combination with radiotherapy: Radiotherapy is a standard treatment modality for oral cancer. Preclinical studies have suggested that combining glucosinolates with radiotherapy may improve the outcomes of radiation treatment. Glucosinolates can sensitize cancer cells to radiation-induced cell death and reduce the radiation dose required for effective treatment.
3. Combination with other dietary compounds: Combining glucosinolates with other bioactive compounds present in the diet has been explored as a strategy to improve therapeutic outcomes in oral cancer. For instance, studies have investigated the combination of glucosinolates with curcumin, a compound derived from turmeric known for its anticancer properties. The combination of these two compounds has demonstrated enhanced anti-proliferative effects and increased apoptosis (programmed cell death) in oral cancer cells.
4. Combination with targeted therapies: Targeted therapies aim to selectively inhibit specific molecular targets involved in cancer growth and progression. Combinatorial approaches involving glucosinolates and targeted therapies have been explored in oral cancer. Glucosinolates have been shown to enhance the efficacy of targeted therapies by modulating key signaling pathways involved in oral cancer. For example, combining glucosinolates with inhibitors of epidermal growth factor receptor (EGFR) signaling has shown synergistic effects in inhibiting oral cancer cell proliferation.

7. Conclusion

By examining the existing literature, this review aims to shed light on the potential of glucosinolates as a promising adjunct therapy for oral cancer. While the in vitro studies demonstrate the anti-cancer effects of glucosinolates, the clinical evidence is limited and further

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research is warranted to establish their efficacy and safety in human trials. Considering their low toxicity and availability in dietary sources, glucosinolates hold great promise as a complementary or adjuvant therapeutic strategy for oral cancer. However, additional research is required to elucidate optimal dosing, formulation, and potential interactions with other medications. The findings of this comprehensive review will aid in guiding future studies and stimulate the development of innovative therapeutic approaches for oral cancer treatment.

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