Senyawa Aktif dari Tanaman Cruciferous dan Efeknya terhadap Kesehatan Gigi dan Mulut

(Cruciferous-derived Bioactive Compounds and Their Effects on Oral Health)

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Abstrak

Gigi dan mulut berada pada keadaan sehat jika seseorang dapat melakukan fungsinya seperti makan, tersenyum, berbicara, bebas dari nyeri kronis, peranyakit dan kelainan. Famili Brassicaceae meliputi sayuran krusiferus telah banyak diteliti mengandung sejumlah besar dari senyawa bioaktif yang bisa digunakan untuk agen untuk menjaga kesehatan gigi dan mulut. Tinjauan ini bertujuan untuk menganalisis senyawa sayuran krusiferus yang memiliki dampak pada kesehatan rongga mulut. Sulforaphane, Indole-3-Carbino (I3C) and Sulforaphene adalah senyawa yang sudah paling banyak diteliti yang dikaitkan dengan pengobatan penyakit rongga mulut. Pada level molekular, senyawa bioaktif krusiferus memiliki efek pada kanker oral, karies, periodontitis, komposisi saliva, dan bau mulut. Tanaman krusiferus menyediakan banyak manfaat untuk kesehatan gigi saat digunakan sebagai sumber makanan dan bahan obat – obatan. Dalam hal melawan kanker oral, I3C menunjukkan perkembangan yang signifikan. Penelitian lebih lanjut bisa dilakukan pada senyawa aktif lain dari tanaman krusiferus dan efeknya dengan mengkombinasikannya.

Kata kunci: Kesehatan gigi dan mulut, Krusiferus, Senyawa bioaktif

Abstract

Oral health is a condition when a person can do functions like eating, smiling, speaking, and being free from chronic pain, diseases, and disorder. The Brassicaceae family, which includes cruciferous vegetables, is believed to contain a large number of bioactive substances that can be utilized as an agent to maintain oral health conditions. This review aims to analyze bioactive compounds in cruciferous vegetables that affect oral health. Sulforaphane, Indole-3-Carbinol, and Sulforaphane are well-known substances being researched as treatments for oral illnesses. At the molecular level, cruciferous bioactive chemicals impacted oral cancer, caries, periodontitis, salivary composition, and malodor in the mouth. Cruciferous plants offer a number of advantages for dental health when used as a food and medicinal tool. In the fight against oral cancer, I3C showed significant advancements. Additional research needs to be done on the many chemicals obtained from cruciferous plants and the effects of their combination.

Keywords: *Bioactive compound, Cruciferous, Oral health*

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A person's overall health, which allows them to eat, speak, smile, and engage in social interactions, is referred to as oral health [1]. Based on WHO, oral health is "a state of being free from chronic mouth and facial pain, oral and throat cancer, oral infection, and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit individual's capacity in biting, chewing, smiling, speaking and psychosocial well-being" [2]. Inadequate nutrition can have an impact on oral health conditions such as dental caries, periodontal disease, oral mucosal disease, and infectious diseases [3].

Vegetables in the Brassicaceae family are cruciferous. It is mostly made up of economically significant vegetable, feed, and spice plants as well as edible oil plants. Broccoli, Brussels sprouts, cabbage, cauliflower, kale, radish, and turnips are among the vegetables in this family [4]. It contains both nutritional and non-nutritive components, both of which are thought to be essential for preserving dental health. One important family of secondary metabolites is nitrogen-containing chemicals, while the two main sulfur compounds are S-methyl cysteine sulfoxide (SMCSO) and glucosinolate (GSL). The colored chemicals flavonoids, anthocyanins, and carotenoids are known to be physiologically active. Significant health advantages are provided by terpenes, polyphenols, coumarins, and therapeutic antioxidant enzymes [5]. Among the advantages of cruciferous vegetables is their anticarcinogenic properties, which protect against specific cancer types [6,7].

This review aims to analyze bioactive compounds with clear chemical structures extracted from cruciferous plants that have been investigated to maintain oral health and advance oral disease treatment options.

RESULT

The cruciferous family contains broccoli, broccoli sprouts, Brussel sprouts, cabbage, collard greens, garden cress, horseradish, kale, kohlrabi, mustard greens, radishes, rutabaga, swiss chard, turnips, turnips greens, bok choy, beet greens, and arugula.

Isothiocyanates (ITC)

ITCs are the major bioactive compounds in cruciferous vegetables responsible for anticancer activity. ITCs are a class of compounds derived from the enzymatic hydrolysis (myrosinase) of glucosinolates (G.L.s), which are sulfur-containing compounds. They can be activated by cutting or chewing vegetables, but heating will eliminate their action [8]. After ingestion of cruciferous vegetables, microbial myrosinase from the gut can release ITCs in the stomach.

Ko et al., 2016, conducted a study in order to determine the Minimum Bactericidal Concentration (MBC) and Minimum Inhibitory Concentration (MIC) of ten ITCs and radish root hydrolysate. The isothiocyanates employed in this study are Allyl ITC, iberin, erusin, sulforaphane, and sulforaphane from the Aliphatic ITC. Aromatic ITC groups are Phenylethyl ITC, Benzyl ITC, Phenyl ITC, and Indolyl ITC group, which consists of Indole-3-carbinol [9,10].

When MIC was tested, eight ITCs demonstrated fair growth inhibition against five strains, except for E. faecalis. Those ITCs were I3C, BITC, PEITC, Erucin, iberin, sulforaphane, and sulforaphane orderly, with I3C as the potent growth inhibitor. For MBC measurement, I3C, BITC, PEITC, erusin, and iberin were bactericidal. They had the same or twice their MIC. On the other hand, sulforaphane, sulforaphane, and AITC were bacteriostatic with MBC less than four timesMIC [10].

Additionally, the study discovered that particular roles (e.g., thiol group and double bond), the length of a hydrocarbon chain, or molecular size affected their antimicrobial activities. Indolyl ITC (which has an indole group), was the most effective inhibitor of oral bacteria growth. Aliphatic ITCs and aromatic ITCs with benene ring were the next most potent inhibitors. Also, double bond existence in chemical structure appeared to advance antimicrobial activity. Other than that, antimicrobial activity depended on the hydrocarbon chain length [10].

After radishes were analyzed, the hydrolysate of the roots contained 15.6% sulforaphane and 82.2% raphasatin, according to the study. The active components of radishes, such as raphasatin and sulforaphene, may have anticancer, antibacterial, antiviral, and antioxidant properties [11]. The minimum inhibitory concentration (MIC) of radish root hydrolysate against S. mutans, C. albicans, and L. casei was 0.188 mg/ml. Raphasatin concentration against S. aureus, S. sobrinus, and E. faecalis was determined to be >0.500 mg/ml. MBC was found to be the same or less than twice MIC (10), indicating that the hydrolysate of radish roots was bactericidal.

Sulforaphane (SFN)

Organosulfur compounds of the isothiocyanate group include SFN (1-isothiocyanato-4-methylsulfinylbutane). A study by Dias, 2013, aimed to comprehend the role of SFN to restore cellular glutathione levels and lower the hyperactivity of circulating neutrophils related to chronic periodontitis. It was an ex vivo study and neutrophils assessed in this study were taken from patients with periodontitis, then SFN was used for pre and post-treatment before laboratory study conducted [8].

The result indicated significant redox disturbance exists in neutrophils of patients with periodontitis and is associated with dysregulation of the inflammatory transcription factor Nrf2. Activation of the redox-sensitive protein ASMase, to promote lipid raft formation and thereby assembly of the NADPH oxidase enzyme was further mediated by a disruption in redox balance [8]. Thus, SFN is thought to lessen the severity of periodontitis.

A study by Alam et al, [9] studied the effect of different types of cruciferous vegetables extracts, which are fresh radish, cabbage, cauliflower, turnip, and broccoli. The previously discussed extracts' bioactive component, SFN, was also examined in relation to the activity of purified hsALDH which its role is to detoxify toxic aldehydes into non-toxic carboxylic acids. A reduced level of hsALDH is a risk factor for oral cancer development. It was also investigated how hsALDH responded to acetaldehyde both with and without SFN.

The result showed out of all the five cruciferous vegetables used in this study, cabbage presented the maximum activating effect on the activity of hsALDH. According to one research rinsing with ethanol-containing mouthwashes causes an increase in the acetaldehyde level in the saliva (20). In the absence of SFN, hsALDH demonstrated virtually no activity towards acetaldehyde. However, the enzyme demonstrated notable activity towards acetaldehyde in the presence of 50 nM SFN. Thus, it is expected that SFN should defend individuals from salivary acetaldehyde-induced toxicity by activating hsALDH to oxidize acetaldehyde. It is prone that consumption of a large number of cruciferous vegetables or SFN supplements can decrease the risk of acetaldehyde-mediated toxicity and the development of oral cancer [9].

Indole-3-Carbinol (I3C)

I3C is found in vegetables such as broccoli, brussel sprouts, cabbage, collards, cauliflower, kale, mustard greens, turnips, and rutabagas. It is formed from glucobrassicin, when these vegetables are cut, chewed, or cooked [21]. Its molecular formula is C_9H_9NO. I3C is rapidly converted in the stomach to various condensation products, chiefly diindolylmethane (DIM). Plasma from humans and rats fed I3C contains no discernible I3C but large amounts of DIM and other metabolites, some of which remain uncharacterized [22].

The anticancer effects of I3C/DIM may be related to many pathways, such as alters during the process of the cell cycle, apoptosis, carcinogen bioactivation, and DNA repair.

A study by Kamal etal., 2018, focuses on the relationships among specific anticancer properties such as cell cycle progression, apoptosis, carcinogen bioactivation, and DNA

repair as a function of the quantity and duration of I3C exposure [11].

The experiment was in vivo and used induced hamster buccal pouch (HBP) carcinogenesis. Induction of OSCC can be successfully done by 7, 12-dimethylbenz[a]anthracene (DMBA) in a hamster buccal pouch (HBP). It was discovered that produced OSCC substantially resembles humans morphological, histological, and biochemical, and molecular characteristics [23].

The study that used I3C as pre-treatment to the hamster by feeding 50 mg/kg a week before the cancer induction demonstrated that I3C was a promising potential chemopreventive agent. It was assured by an increase in cytochrome Bax expression in microscopic examination that explains tumor cell proliferation and apoptosis inhibition and a decrease of epithelial dysplasia in histologic examination in the hamster group with I3C pre-treatment. Moreover, Bcl-2 exhibited weak positive cytoplasmic expression throughout the dysplastic epithelial layers in other I3C-treated tissue sections [11].

A study by Hammerschmidt-Kamper et al., 2017 aimed to determine how oral dosing of one such AhR-ligand, I3C, affects oral tolerance and whether this correlates with increased food allergies. They examined the effects of I3C-licensed oral tolerance under conditions that wouldnot normally induce this immunosuppressive state. They also tested the effects of dietary I3C on peanut allergy [12].

The study was conducted in vivo using mice fed food containing I3C daily. I3C used in the study was its metabolites 3',3' dundolomethane (DIM) and indole (3,2-carbazol (ICZ). It was measured in blood serum samples by feeding with 2g/kg I3C containing chow for a week. To determine gene induction in the small intestine, mice were provided by gavage containing Tetrachlorodibenzo-p-dioxin (TCDD), a polychlorinated dibenzo-p-dioxin, diluted in olive oil. Model antigen ovalbumin (OVA) feeding protocol was developed so that the OVA dose was no longer high enough to induce oral tolerance in mice. Peanut extracts were also prepared and checked for protein content bicinchoninic acid analysis. Mice were then sacrificed for organ resections [12].

The results demonstrated that oral induction leads to the induction of the cyp1a1 along the murine small intestine. The induction also did not subside upon long-term exposure to a comparatively moderate dose, indicating constant high AhR-activity by the diet. The study also investigated the effects of I3C on the vital immune function of oral tolerance and found that dietary exposure to I3C licensed oral tolerance under conditions that would not normally induce this immunosuppressive state. For the effects of dietary I3C on peanut allergy, feeding I3C ameliorated the allergic symptoms in our mice but not the sensitization (antibody formation)[12].

Benzyl Isothiocyanate (BITC)

BITC is an isothiocyanate member of benzenes [13] with molecular formula C8H7NS. A study by Yeh et al., 2016, examined BITC on OSCC. Human oral cancer OC2 cells were used at physiologically relevant concentrations, on cell cycle arrest, apoptosis, free radicals generation, glutathione (GSH), and GSH/oxidized glutathione (GSSG) ratio, and signal transduction pathways. In addition, the toxic effects of BITC on human peripheral blood mononuclear cells (PBMCs) were investigated [14].

The results have shown that diminished GSH levels increase cellular vulnerability toward GSH redox stress and oxidative DNA damage, resulting in G2M cell cycle arrest and apoptosis of human oral cancer cells. The BITC induces apoptosis of human cancer cells by causing GSH redox stress and other cellular redox stress. It was also found that BITC was more potent than PEITC. BITC thought to effectively killed oral cancer cells with minimal toxicity to normal cells.

The study results revealed BITC-induced reactive oxygen species/reactive nitrogen species (ROS/RNS), O2, and (Nitric Oxide) NO generation and GSH depletion. While, excessive ROS/RNS can cause oxidative damage and induce cell apoptosis or necrosis. BITC-induced 8-Hydroxy-2'-deoxyguanosine (8-OHdG) production and DNA damage results in the activation of ATM and the downstream gene Chk2, resulting in p53 activation. Chk2 and p53 regulate an array of target genes, including the induction of G2/M phase arrest and apoptosis. All in all, BITC causes cellular redox stress and ROS/RNS and NO generation, which leads to redox stress-mediated DNA damage and ATM/chk2/p53, a pathway involved in DNA damage repair, dependent G2/M arrest, disruption of the mitochondrial membrane potential, and triggering of redox stress-dependent apoptosis [14].

Phenethyl Isothiocyanate (PEITC)

PEITC can be obtained from watercress, broccoli, turnips, and radish [15]. Its molecular formula is C_9H_9NS. Another study by Yeh et al. 2014, performed an experiment of the molecular mechanism and anticancer potential of PEITC in OSCC cells with various p53 statuses. Numerous studies have described p53 alteration as an early event in oral cavity carcinogenesis, and a mutated p53 expression is often observed in noncancerous epithelium adjacent to OSCC [24]. In this study, three sets of OSCCs (OC2, SCC-4, and SCC-25) expressing a functional p53 mutant were used to investigate the effect of varying p53 status on PEITC-induced cell cycle arrest and apoptosis. In addition, they evaluated the

therapeutic selectivity of PEITC and its potential for use in the treatment of OSCCs with a functional p53 mutant. The study intended to determine the toxic effects of PEITC on normal human cells, such as human peripheral blood mononuclear cells and fibroblasts.

The result showed PEITC caused GSH depletion, thus leading to oxidative DNA damage and p53- related G2/M arrest and apoptosis in oral cancer cells. PEITC–induced anticancer effects were suppressed in the presence of the p53 inhibitor pifithrin-a and the antioxidants N-Acetyl Cysteine and GSH. The experiments also demonstrated that PEITC effectively kills oral cancer cells with very low toxicity to normal cells: PEITC-induced ROS and NO generation. The results also prove that the significantly greater comet tail length observed in OC2 cells when exposed to PEITC over time indicates DNA damage. PEITC may selectively target p53 and even its mutants in oral cancer cells because apoptosis is observed in OSCCs expressing a functional p53 [15].

Allyl Isothiocyanate (AITC)

The organosulfur chemical, identified as AITC, is derived from the seeds of brown Indian mustard (Brassica juncea) and black mustard (Brassica nigra). A study by Chang et al., 2020, investigated AITC on OSCC. The study examined the possible molecular mechanisms of AITC anticancer effects to find an alternative therapeutic against cisplatin resistance in OSCC patients. As the CAL27-cisplatin resistant (CAR) oral cancer cell line developed unique resistance to cisplatin treatment, it is examined to study the antitumor properties of AITC [16].

The anticancer mechanism of cisplatin, the most widely-used chemotherapeutic agent, involves the generation of DNA lesions followed by the activation of the DNA damage response and the induction of mitochondrial apoptosis. The result of 4',6-diamidino-2-phenylindole (DAPI) staining suggested that AITC induced CAR cell apoptosis. Furthermore, the western-blotting exam demonstrated that the key molecules which positively regulate mitochondrial–dependent intrinsic apoptotic pathways were upregulated by AITC. The finding is unique; AITC decreased the viability and induced cell death of human cisplatin-resistant OSCC CAR cells, induced DNA fragmentation, and enhanced activities of caspase-3 and caspase-9. Thus, it inhibited AktmTOR,a pathway regulating the cell cycle, and proliferation signaling, and promoted mitochondria-dependent CAR cell apoptosis [16].

A study by Tian et al., 2013, aimed to evaluate the in vivo effect of chewing gum containing AITC alone and combined with zinc salts. The test was conducted on reducing volatile sulfur compounds (VSCs). The study used 15 healthy volunteers between 20-50 who chewed either an experimental or a placebo gum for 12 minutes. Their mouth air was analyzed for VSCs by a gas chromatograph at baseline, immediately after chewing, and at 60, 120, and 180 minutes after treatment [17].

According to the examination's findings, chewing gum containing 0.01% allyl isothiocyanate and 0.1% zinc lactate removed 89%, 55.5%, 48%, and 24% of the total VSC content in the instantaneous, two, and three-hour time frames, respectively. The current study indicated that chewing gum containing a low level of AITC can effectively reduce oral malodor. The effect is reinforced when AITC is combined with a low level of zinc lactate without impacting the sensory taste [17]. Table 1 summarizes some cruciferousbioactive compounds studied related to oral health.

DISCUSSION

As oral health is obtained by maintaining oral hygiene is crucial to achieving good oral health. Gingival inflammation affects over 90% of the population. If treated, the prognosis is good; if left untreated, it can worsen and lead to tooth loss and periodontitis [25]. Periodontal disease is the second most urgent global oral disease concern and the seventh-most frequent non-communicable disease globally [26]. The burden of chronic non-communicable diseases repeatedly decreases older people's oral health-related quality of life (OHRQoI) [27]. Chronic periodontitis is a multifactorial infectious disease, represented by the manifestation of the loss of periodontal supporting tissue slowly and irreversibly in a period. Although the fundamental mechanisms of chronic periodontitis are left unclear, peripheral blood neutrophil hyperactivity (unstimulated cells) and reactivity (to a stimulus) are crucial elements of the disease. SFN lowered the severity of periodontitis by interrupting neutrophil cellular interaction [8].

The functions of saliva to protect oral tissue, beginning with the digestion of starch and declining the risk of dental caries and oral candida infection, are widely known. Recently, additional functions of the salivary gland have been identified, that is, secreting active substances such as nerve growth factors, vasoactive peptides, and regulatory peptides [28].

Table 1. Research Progress on Cruciferous Compounds in Oral Health

Compounds	Molecular Formula	Results	References
Isothiocyanates(ITC)			
Sulforaphane(SFN)	$C_6H_{11}NOS_2$	Prior to the onset of chronic periodontitis, SFN pretreatment functioned to inhibit Nrf2-dependent pathways that may be the source of circulating primary neutrophil hyper-reactivity.	(8)
		The vital detoxifying enzyme in the mouth cavity, human salivary aldehyde dehydrogenase (hsALDH), was activated by SFN.	(9)
		SFN lessen the occurrence of oral pathogen growth.	(10)
Indole-3-Carbinol, Glucosinolate (I3C)	C_9H_9NO	- I3C therapy reduced epithelial dysplasia in the buccal pouch of hamsters used as OSCC mimics. - In groups receiving I3C treatment, there was an increase in cytochrome Bax expression, which suggested that tumor cell growth and apoptosis were inhibited.	(11)
		I3C stimulated AhR in the gut and aided the generation of the anti-inflammatory micro-environment, so vital immune functions of oral tolerance may inhibit food allergies	(12)
		Reduce growth inhibition of oral pathogens	(10)
Benzyl isothiocyanate (BITC)	C8H7NS	- BITC limits OC2 cell proliferation while presenting less of a toxicity to normal cells. - BITC generates G2M phase arrest and apoptosis - BITC-triggered cell death by redox-dependent control	(14)
		Reduce growth inhibition of oral pathogens.	(10)
Phenethyl isothiocyanate(PEITC)	C_9H_9NS	- PEITC prevented cell growth in OSCCs - PEITC triggered G2M phase arrest and apoptosis - Induction of p53 for PEITC-induced G2M phase arrest and apoptosis - Induction of the ATM-Chk2-p53 pathway by PEITC-induced oxidative DNA damage	(12)
		Reduce growth inhibition of oral pathogens.	(10)
Allyl Isothiocyanate (AITC)	C_4H_5NS	- AITC reduced the CAL27-cisplatin-resistant oral cancer cell line's viability and caused cell death. - AITC-induced DNA fragmentation and upregulated caspase-3 and caspase-9 expression in CAR cells - AITC enhanced CAR cell apoptosis that is dependent on mitochondria and suppressed proliferative signaling	(16)
		Chewing gum with a low AITC content is capable of reducing oral malodor	(17)
		Reduce growth inhibition of oral pathogens.	(10)
Other ITC			
Sulforaphane	$C_6H_9NOS_2$	Reduce growth inhibition of oral pathogens.	(10)
Iberin	$C_5H_9NOS_2$		
Eurecin	C6H11NS2		
Raphasatin	$C_6H_9NS_2$		

Moreover, saliva contains enzymes such as aldehyde dehydrogenase (hsALDH), a primary class 3 ALDH that keeps a healthy oral cavity that detoxify harmful aldehydes into non-toxic carboxylic acids. A reduced level of hsALDH is a risk factor for oral cancer development [29], and SFN contributed to increasing the production of hsALDH [9].

Healthy people are frequently exposed to foreign proteins but do not develop an immune response, unlike people suffering from allergies. Food allergies can be understood as the breakdown of oral tolerance, resulting in systemic anaphylaxis and frequently a type I allergic response. Itching, abdominal pain, bronchospasms, and even anaphylactic shock may result from food allergies. As for the oral cavity, it can be formed as dry mouth or angioedema [30].

Oral tolerance may be determined as oral antigen exposure followed by antigen-specific suppression of cells and antibody-mediated immune response [31]. Therefore, preliminary gastrointestinal exposure to an antigen often reduces reactivity to further local orsystemic exposure to the same antigen [32,33]. A complete understanding of oral tolerance mechanisms will help answer the critical problem of reducing food allergy prevalence through primary prophylaxis (via natural tolerance development). Also, to set up new strategies for food allergy treatment (via induced tolerance) [31]. I3C was proven to have a role in developing an anti-inflammatory milieu, so vital immune functions of oral tolerance may inhibit food allergies [12].

Oral cancer is the 16th most common

malignancy and the 15th leading worldwide cause of death. The incidence of oral cancer (age-adjusted) worldwide is four cases per 100,000 people [34,35]. Surgical removal of extensive oral malignancy tumors inevitably results in losing vital functions such as swallowing, speech, and senses of taste and smell [36]. The consequences may affect patients' psychological, physical, social, and emotional well-being andquality of life [37]. Poor oral hygiene (POH) may contribute to oral carcinogenesis [38]. Factors contributing to POH include irregular teeth brushing habits, less number of dental visits, poor socioeconomic status, lower education, and tobacco and alcohol consumption [39]. Other than POH, chronic mucosal trauma and poor nutrition also aid in developing oral cancer.

About 90% of people with oral cancer are diagnosed with oral squamous cell carcinoma (OSCC), and the survival rate has hovered around 55-56% [40]. Smoking, drinking habits, and ultraviolet radiation are major etiological and predisposing factors for OSCC. Surgical resection to remove tumor lesions is the main treatment for OSCC.

The treatment plan may integrate radiotherapy and chemotherapy into the regimen for those with advanced stages of tumor or adverse histological features [41]. Some in vitro studies [14-16] have already given a promising result that BITC, PEITC, and AITC altered cancer development. Therefore, it is highly recommended that in vivo and human clinical trials be developed. On the other hand, I3C demonstrated a promising result in vivo study [11], suggesting that I3C should be used for clinical trials study.

Oral malodor is a significant social and psychological problem for the general population. Although bad smelly breath primarily represents a source of embarrassment or annoyance, the VSC most responsible for halitosis is potentially damaging to the tissues in the mouth. It can lead to periodontitis [17].AITC that adds to chewing gum at a low level could reduce halitosis [17].

The prevalence of tooth decay globally is nearly 90% of adults ages 20 to 64 years have had decay in their teeth. Oral bacteria modify sugar and starch into acids, initiating calcified dental plaque [42]. Dental plaque control is an essential strategy for preventing dental caries. Toothbrushing is the most accepted method for controlling plaque, but if this is not enough to remove dental plaque, antimicrobial agents are needed to kill oral pathogens [43]. The growth of *Streptococcus mutants, Streptococcus sobrinus, Streptococcus aureus, Enterococcus faecalis, Lactobacillus casei,* and *Candida albicans,* which are the common pathogens found in oral tissuewere proven inhibited by I3C, BITC, PEITC, erucin, iberin, SFN, sulforaphene, and raphasatin. They may be developed as ingredients in antimicrobial and antiseptic solution in dentistry [10].

This study reveals that the most common oral disease studied that was examined using cruciferous bioactive compounds is oral cancer. The most frequent cruciferous vegetables examined are fresh radish. Some cruciferous vegetables that were least studied and discussed are collard greens, garden cress, kohl rabi, swiss chard, beet greens, and arugula. The most common bioactive compound studied is sulforaphane. There are some bioactive compounds that havebeen studied in medicine but not in oral health related which are a-Naphthylisothiocyanate, S-methyl-methanethio sulfonat, and brassinin. Lastly, the most popular study method used to analyze cruciferous bioactive compounds related to oral health is by in vitro study.

Most of the researchers were encouraged to study cruciferous-derived compound because of previous data have been showing promising results. One study showed SFN accelerates acetaldehyde metabolism by inducing ALDHs and hence may protect individuals who are alcohol intolerant against acetaldehyde toxicity [44]. Furthermore, it is believed that modulation of important enzymes like quinone reductase, glutathione *S*-transferase, ALDHs and ribonucleoside diphosphate reductase by natural bioactive compounds or synthetic chemical compounds may be a significant component of their anticarcinogenic action [9]. So Alam et al, 2016 studied SFN with 5 other cruciferous vegetables in hsALDH enzyme activation. Then, one study revealed that 2,3,87,8,8-tetrachlorodibenzo-p-dioxin (TCDD), an environmental pollutant, destabilized oral tolerance in mice [45]. Despite the previous tolerization, TCDD-treated mice produced antibodies against the model antigen OVA after several boosting immunizations. Then, Hammerschmidt-Kamper et al. investigated oral tolerance against OVA from ligand I3C [10]. Showing a surprising yet positive result, I3C demonstrated oral tolerance activation and an increased anaphylactic score in peanut allergy. Further investigation into chemicals derived from cruciferous plants is required due to their potential as remedies for oral and systemic health issues.

Furthermore, the development of compounds derived from cruciferous plants against cancer indicates a more advanced product. Research on the clinical use of SFN in humans is necessary. This compound's high availability, tolerability, and effectiveness as a chemoprevention agent in preclinical models [46]. A few clinical trials have been carried out tenting the suitability of oral supplementation of SFN for cancer chemoprevention and in combination with other anticancer drugs. In the prostate

cancer case, a study demonstrated a phase II clinical trial in patients with biochemical recurrence after prostatectomy. The outcome showed that compared to pre-treatment, patients who received oral administration of SFN showed a lengthening of the on-treatment prostate-specific antigen doubling time [47]. In a breast cancer case, there is a recent phase II clinical trial. The results showed that the administration of SFNas an adjuvant enhanced the efficacy of doxorubicin against in vivo breast cancer [48]. Other than SFN, PEITC, and BITC also undergo human clinical trials against breast cancer [49]. Moreover, combination therapy of AITC and radiation treatment showed an increased cell killing in non-small cell lung cancer rather than single agent treatment [50]. Therefore, research on cruciferous-derived chemicals against oral cancer is currently ongoing both in vitro and in vivo; furthermore, combination therapy and clinical trials need to be advanced.

To our knowledge, limited studies of cruciferous-derived compounds are still investigated on oral hygiene products. AITC added to chewing gum is one potential compound for answering oral health problems. The author suggests further research on cruciferous compounds as ingredients in products used to maintain oral hygiene.

Plants of the Brassica family have long been known to have health benefits. Both as a diet or as therapeutic agents, potential cruciferous plants have various benefits for oral health. Further studies on bioactive compounds that have not been studied related to oral health, such as α-Naphthylisothiocyanate, S-methyl-methanethiosulfonat, and brassinin should be accomplished. Moreover, studies about common bioactive compounds combined with other agents should also be developed.

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