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Dietary Organosulfur-Containing Compounds and Their Health-Promotion Mechanisms

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Abstract

Dietary organosulfur-containing compounds (DOSCs) in fruits, vegetables, and edible mushrooms may hold the key to the health-promotion benefits of these foods. Yet their action mechanisms are not clear, partially due to their high reactivity, which leads to the formation of complex compounds during postharvest processing. Among postharvest processing methods, thermal treatment is the most common way to process these edible plants rich in DOSCs, which undergo complex degradation pathways with the generation of numerous derivatives over a short time. At low temperatures, DOSCs are biotransformed slowly during fermentation to different metabolites (e.g., thiols, sulfides, peptides), whose distinctive biological activity remains largely unexplored. In this review, we discuss the bioavailability of DOSCs in human digestion before illustrating their potential mechanisms for health promotion related to cardiovascular health, cancer chemoprevention, and anti-inflammatory and antimicrobial activities. In particular, it is interesting that different DOSCs react with glutathione or cysteine, leading to the slow release of hydrogen sulfide (H_2S), which has broad bioactivity in chronic disease prevention. In addition, DOSCs may interact with protein thiol groups of different protein targets of importance related to inflammation and phase II enzyme upregulation, among other action pathways critical for health promotion.

1. INTRODUCTION

In food and nutrition, dietary organosulfur-containing compounds (DOSCs) are known for their unique flavoring properties and health-promoting functions. Herein, DOSCs exclude sulfur-containing amino acids such as cysteine and methionine. DOSCs are found in many types of foods such as fruits (e.g., durian), edible fungi, and vegetables belonging to the *Allium* genus and Brassicaceae, Fabaceae, and Moringaceae families (Liang et al. 2015a, Qin et al. 2020, Schmidberger & Schieberle 2020, X. Wang et al. 2018, Waterman et al. 2014). Although their characteristic flavors have been explored as natural food-flavoring agents, the focus of this review is on their health-promotion activity, as numerous researchers have demonstrated that DOSCs could prevent a broad spectrum of chronic diseases (Morales-González et al. 2019, Pan et al. 2018, Putnik et al. 2019, Tocmo et al. 2015). For example, DOSCs in *Allium* have antioxidant, anti-inflammation, anticancer, antiaging, antimicrobial, and antifungal properties (Batiha et al. 2020, Ryu & Kang 2017). In addition, they have also been reported to boost the immune system and reduce the risk of cardiovascular diseases and diabetes (Morales-González et al. 2019, Yuan et al. 2017). In the Brassicaceae family, isothiocyanates (ITCs), a secondary metabolite from hydrolysis of glucosinolates (GLs) via the action of myrosinase, have received attention because of their cancer chemoprevention activity (Bo et al. 2016, Favela-González et al. 2020, Pawlik et al. 2017), which could be due to their ability to suppress phase I and promote II enzyme activity and/or epigenetic events, including histone modification and DNA methylation (Lu et al. 2020, Singh et al. 2020, Yeh et al. 2016).

Unlike other secondary metabolites such as flavonoids and saponins, one salient feature of DOSCs is that they are highly reactive and undergo complex transformations, triggered by enzymes and heat, into diverse products that can further undergo reactions with biological molecules such as glutathione (GSH). In intact plant tissues, DOSCs are mostly present as nonvolatile hydrophilic precursors such as GLs and amino acids (e.g., alliin and djenkolic acid). Upon disruption of these tissues, endogenous enzymes come into contact with the precursors and convert them into lipophilic DOSCs that are often volatile and endow vegetables with their characteristic flavors. These metabolites (e.g., ITCs, allicin, methanedithiol) could further undergo thermal transformations during food processing to give rise to complex (poly)sulfides. The diversity of the DOSCs poses a great challenge to establishing the structure and activity relationship accounting for their health-promotion function. Herein, we analyzed recent studies on DOSCs, with the aim of providing a concise picture of the interrelationship of DOSCs in a specific group of foods so that the cause-and-effect relationship that leads to their bioactivity can be better understood for cardiovascular health, cancer chemoprevention, anti-inflammation, and antimicrobial activities.

2. OVERVIEW OF MAJOR DIETARY ORGANOSULFUR-CONTAINING COMPOUNDS

2.1. Dietary Organosulfur-Containing Compounds in Alliums

Common alliums used as seasonings and vegetables include chives, onions, garlic, and leek. The DOSCs in the intact fresh alliums are mainly S-alk(en)yl-L-cysteine-sulfoxides (ACSOs) with a molecular formula of $R\text{-}S(O)CH_2CH(NH_2)CO_2H$. The alkyl substituents vary according to plant species, and the most extensively studied are garlic [R is dominantly allyl ($CH_2 = CH\text{-}CH_2\text{-}$)] and onion [R is propenyl ($CH_3\text{-}CH = CH\text{-}$)]. The isomeric R groups dictate their metabolic products formed by the action of alliinase (Fujii et al. 2018, Huang et al. 2019).

When garlic is crushed, alliin mixes with alliinase and is converted to allicin, which is reasonably stable and used in quality assurance for commercial garlic supplements. Allicin is thermally

transformed to various oil-soluble polysulfides, including diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS), which are the main components in garlic oil (Liang et al. 2015a, Tocmo et al. 2017b). These polysulfides can also be formed in uncooked garlic homogenates containing thiosulfinates with different substituents (e.g., methyl, 1-propenyl, and 2-propenyl) (Zhang & Parkin 2013). For onion, isoalliin is converted by alliinase and lachrymatory factor synthase (LFS) to propenylsulfoxide (Eady et al. 2008). Other onion-related DOSCs include minor amounts of disulfides and polysulfides with a formula of $R(S)_nR'$ (R and R' = propyl or methyl 1-propenyl) (Kim et al. 2016a, Putnik et al. 2019, Tocmo et al. 2015). The amount of DOSC from onions is significantly affected by species, extraction condition, and growing area.

2.2. Dietary Organosulfur-Containing Compounds in Cruciferous Vegetables

The fresh and intact tissues of cruciferous vegetables are rich in GLs, which are readily converted by myrosinase into ITCs (R-NCS: R, alkyl, allyl, or aromatic substituents; NCS, isothiocyanate), which are believed to be responsible for health-promotion benefits (Favela-González et al. 2020). Different cruciferous vegetables have ITCs with variable substituents (R-NCS). For example, broccoli is rich in sulforaphane (SFN) (Sarvan et al. 2017), whereas garden cress and watercress are rich in benzyl ITC (I BITC) and phenylethyl ITC (PEITC), respectively (Jang et al. 2010, Yeh et al. 2016). Both GLs and ITCs may have aliphatic, aromatic alkyl, and aromatic subchains. In addition to GLs and ITCs, *S*-methyl cysteine sulfoxide (SMCSO), or methiin, is found in cruciferous vegetables. It generally contributes to the distinct spicy and pungent aroma of uncooked cruciferous vegetables (Manchali et al. 2012). Consequently, DOSCs in processed cruciferous vegetables include dimethyl thiosulfinate, dimethyl thiosulfonate, and methyl sulfenic acid, all derived from SMCSO by the action of cystine lyase. Thermal treatment results in the formation of dimethyl disulfide and dimethyl trisulfide (DMTS) via the degradation of methyl methanethiosulfinate, which is generated by the condensation of methyl sulfenic acid (Tocmo et al. 2015).

2.3. Dietary Organosulfur-Containing Compounds in Stinky Beans and Djenkol Beans

The predominant DOSC in stinky beans and its close relative djenkol beans is djenkolic acid $[CH_2(SCH_2CHNH_2CO_2H)_2]$. In ripe stinky bean (but not in djenkol bean), djenkolic acid and its derivative, *N*-acetyl-djenkolic acid, are transformed by the C-S lyase followed by oxidation of formed methanedithiol $[CH_2(SH)_2]$ to generate cyclic polysulfides (e.g., 1,2,4-trithiolane, 1,3,5-trithiane, 1,2,4,6-tetrathiepane, and 1,2,3,5,6-pentathiepane), which are responsible for the strong pungent smell of the ripe stinky bean (Frerot et al. 2008, Izzah Ahmad et al. 2019, Tocmo et al. 2015). Other identified minor volatile DOSCs in stinky beans include 3,5-dimethyl-1,2,4-trithiolane, 1,2,4,5-tetrathiocane, 1,2,4,5-tetrathiane, 1,2,3,4,5,6-hexathiepane, and 1,2,4,5,7,8-hexathionane (Frerot et al. 2008, Gmelin et al. 1981, Tocmo et al. 2016). Unripe stinky beans do not have an offensive odor, presumably due to the absence of the djenkolic acid lyase.

2.4. Dietary Organosulfur-Containing Compounds in Shiitake Mushrooms and Truffles

Shiitake is one the most consumed mushrooms worldwide and truffles are treasured foods partially due to their flavors arising from DOSCs. In raw shiitake, a total of 18 DOSCs were identified, with high levels of 1-propanethiol, 1,2,4,5-tetrathiane, 1,2,3,5-tetrathiane, and 1,2,4-trithiolane (Schmidberger & Schieberle 2020). Among them, 1,2,4-trithiolane is the key aroma compound

and provides shiitake mushrooms with woody characteristics (Qin et al. 2020). These aroma compounds are most likely formed by the action of lyase on sulfide-containing amino acid precursors (Schmidberger & Schieberle 2020). The truffle *Tuber magnatum* contains 2,4-dithiapentane ($CH_3SCH_2SCH_3$) as its main aroma compound as well as other polysulfides (Mustafa et al. 2020). Methionine is the precursor to these volatile sulfides formed by the action of methionine lyase (Splivallo et al. 2011).

2.5. Dietary Organosulfur-Containing Compounds in Durian

In Southeast Asia, durian is one of the most recognizable fruits because of its distinct shape, texture, and offensive (to some) flavor, which is attributed to organosulfur compounds (Mohd Ali et al. 2020). A study by Voon et al (2007) reported that organosulfur compounds in the Chuk durian variety accounted for 50% of total volatiles, whereas the organosulfur compounds accounted for only 28% in the D101, D24, and MDUR78 durian varieties. In addition, the compositions of organosulfur compounds in durian are dependent on the growing areas of the durian trees. The major DOSCs in durian are 1-propanethiol, diethyl disulfide, diethyl trisulfide, ethyl isopropyl disulfide, dipropyl disulfide, and 3,5-dimehtyl-1,2,4-trithiolane (Lu et al. 2017c, Mohd Ali et al. 2020). The precursors of these volatile DOSCs are sulfur-containing amino acids (Fischer & Steinhaus 2020) that are dependent on the genetics of the durian (Teh et al. 2017). Methionine γ-lyase mediated the transformation of methionine and ethionine into their respective thiols, which were further oxidized into odor-active polysulfides (Fischer & Steinhaus 2020).

3. IMPACTS OF FOOD PROCESSING METHODS ON THE TRANSFORMATION OF DIETARY ORGANOSULFUR-CONTAINING COMPOUNDS

Food processing methods can induce a series of reactions mediated by enzymes, heat, oxygen, and microbes on DOSCs originally found in plant tissues and result in the formation of diverse consumable DOSC end products. The yields of specific types of organosulfur compounds are highly dependent on the processing methods and conditions. Understanding how these DOSCs interconvert would allow us to rationally design processing methods that enrich specific DOSCs in the ready-to-eat food products made from these organosulfur-rich raw materials (e.g., onion, garlic, cruciferous vegetables, stinky bean, djenkol bean, mushroom, truffle, and durian) to achieve the desirable health-promotion functions.

3.1. Transformation of Dietary Organosulfur-Containing Compounds in Onion

Onion has been used as a medicinal plant to treat or relieve symptoms of diseases such as tumors and insect bites, and the rich bioactive compounds, particularly flavonoids and organosulfides, may be responsible for this activity (Teshika et al. 2019). ACSOs in raw onion may prevent chronic diseases such as hypertension (Bahadoran et al. 2017, Nicastro et al. 2015). To preserve the ACSOs from degradation, enzymes are deactivated before the onion is homogenized. However, if the metabolites are desired instead of ACSOs, a homogenization step is performed on raw onion to maximize the formation of 1-propenesulfenic acid ($CH_3CH = CHSOH$), which is a key intermediate to some organosulfur-containing derivatives (**Figure 1a**). Although LFS isomerizes 1-propenesulfenic acid to propanethial-*S*-oxide, it could be transformed into other DOSCs such as thiosulfinates (isoallicin), cepaenes, zwiebelanes, bis-sulfines, cepathiolanes, and allithiolanes (Štefanová et al. 2019). Because the LFS pathway led to the formation of the end
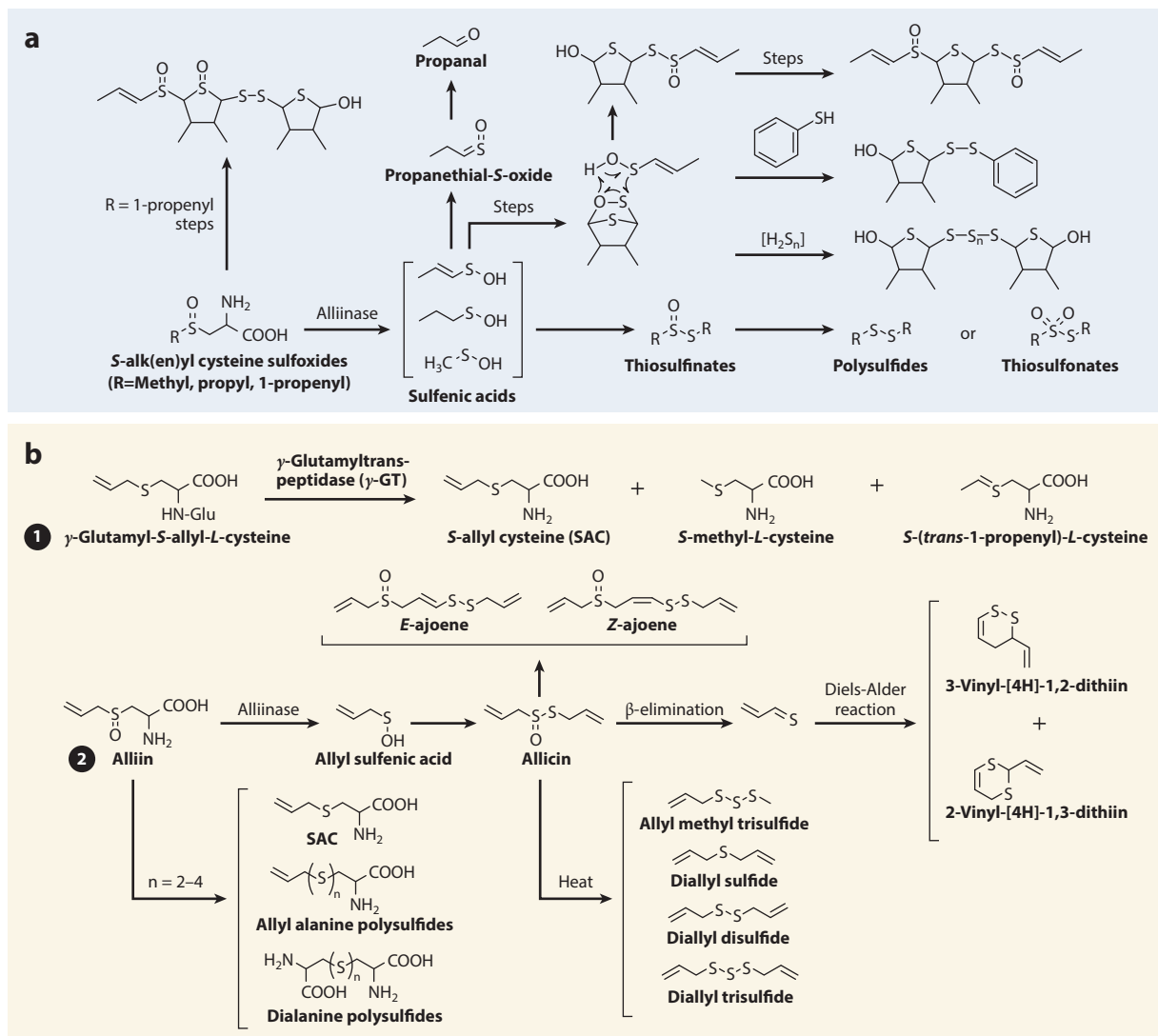
Figure 1

Transformations of main dietary organosulfur-containing compounds in (*a*) onion and (*b*) garlic during thermal processing. Figure adapted with permission from Block et al. (2018) and Tocmo et al. (2015).

product propionaldehyde (after hydrolysis of propanethial-*S*-oxide) and inorganic sulfur species, it is an undesirable pathway that suppresses the formation of bioactive organosulfides through other pathways. Therefore, to direct the conversion of isoalliin to bisthiolane polysulfides, tear-less onion (onion with suppressed LFS) was used (Aoyagi et al. 2021). Directed self-condensation of two 1-propenesulfenic acids forms *S*-(1-propenyl) 1-propenethiosulfinate, which undergoes intramolecular cycloaddition and rearrangement to generate cepathiolane and thiolanopolysulfide. It has been reported that both cepathiolane and thiolanopolysulfide exhibited moderate activity for inhibition of cyclooxygenase (COX)-1 (Aoyagi et al. 2021, Štefanová et al. 2019).

Various heat treatments (e.g., boiling, frying, steaming, and microwaving) have different effects on the profiles of ACSOs in the finished products of onion. ACSO concentration could increase more than 500% via frying, steaming, or microwaving but decrease 33–69% via boiling (Kim et al. 2016a). It has been suggested that the increase of ACSOs was due to elevated activity of several enzymes, particularly γ-glutamyl peptidase and oxidase, at higher temperatures. The former enzyme catalyzes the hydrolysis of γ-ʟ-glutamyl-*S*-(*trans*-1-propenyl)-ʟ-cysteine to *S*-alk(en)yl-ʟ-cysteine, which is then converted into ACSOs if the temperature is moderated so that alliinase is not deactivated.

3.2. Transformation of Dietary Organosulfur-Containing Compounds in Garlic

Although it is not surprising that the levels of alliin or its precursor vary according to the specific cultivar of garlic, there is much less study on the health benefits of alliin compared to allicin. Recent studies have shown that alliin may have beneficial activities for relieving metabolic syndrome (Li et al. 2021) and modulating inflammation induced by diet in obese mice (Sánchez-Sánchez et al. 2020). To enhance the alliin levels in garlic, the enzymes of the whole garlic bulb need to be deactivated during food processing or cooking (e.g., boiling the whole garlic in soup, which is common practice in some dishes).

Allicin has been used as a quality control standard for garlic supplements. To enrich allicin in garlic, special care must be taken in the sample preparation of allicin-enriched garlics (Lawson & Gardner 2005). The thermal-processing conditions, such as temperature, time, pH, and status of the food matrix, may affect the activity of alliinase and therefore the yields of allicin. Surprisingly, high-pressure processing can reduce the alliinase activity. Because there are some disputes regarding the health benefits of allicin based on clinical studies (Gardner et al. 2007), it has been suggested that other organosulfides may be the active compounds in garlic. Upon thermal treatment, allicin is converted into acyclic sulfides such as DADS, DATS, and ajoenes (*E*- and *Z*-4,5,9-trithiadodeca-1,6,11-triene-9 oxides) and cyclic sulfides such as dithiins (e.g., 2-vinyl-4H-1,3-dithiin and 3-vinyl-4H-1,3-dithiin) (**Figure 1*b***) (Fujii et al. 2018, Tocmo et al. 2017b).

The relative concentrations of these compounds would be highly dependent on the conditions of processing. Tocmo et al. (2017b) found that a short boiling time (6–10 min) increased the levels of linear polysulfides (allyl disulfides and trisulfides) but that prolonging boiling time to 30 min decreased their levels. In addition, the levels of ajoenes and cyclic sulfides declined gradually during boiling treatment. These results indicated that a shorter cooking time may help retain high levels of acyclic polysulfides. Besides enzymatic transformation, alliin could be thermally degraded to numerous organosulfur derivatives, including allyl alanine sulfides (disulfide, trisulfide, and tetrasulfide) and dialanine sulfides (disulfide, trisulfide, and tetrasulfide), apparently through deoxygenation and disulfide bond formation (**Figure 1*b***). These nonvolatile polysulfides are of interest for their flavor and bioactivity.

Garlic contains smaller amounts of isoalliin than does onion. Interestingly, garlic does not contain LFS. When isoalliin in garlic is fragmented by alliinase to 1-propenesulfenic acid, it is not isomerized to its sulfoxide. Instead, it undergoes self-condensation to become isoallicin (**Figure 1*a***), which could proceed through a series of reactions, including isomerization and cycloaddition to form ajothiolanes (Block et al. 2018), and this may alter its health benefits.

Fermentation of garlic was found to affect the transformation of organosulfides, as Kim et al. (2016b) found that *Saccharomyces cerevisiae*, *Monascus pilosus*, and *Lactobacillus plantarum* fermentation on garlic increased the level of *S*-alk(en)yl-ʟ-cysteine but reduced the level of γ-glutamyl peptide, likely due to peptidase action. Tocmo et al. (2017a) evaluated the changes of DOSCs in garlic fermented with *L. plantarum* (LP115) and found that allicin and vinyl dithiin levels

decreased and DATS levels increased. Although fermentation is a common processing method for garlic (e.g., pickled garlic), little is known about the DOSC profiles and their respective health benefits and flavor activity. Future work should focus in this direction.

3.3. Transformation of Glucosinolates in Cruciferous Vegetables

When cruciferous vegetables are consumed as salad (mostly in the Western diet), the GLs are processed through the mouth and gastrointestinal (GI) tract, particularly by the gut microbiota, and eventually transformed into ITCs. The chewing of raw broccoli leads to the formation of SFN in the mouth and the SFN is not affected in the stomach or other parts of the GI tract because myrosinase is deactivated in the acidic stomach environment (Sarvan et al. 2017). In Asian countries, cooked broccoli is more commonly consumed than is raw broccoli. Numerous studies have shown that short-time (2–3 min) cooking can increase the levels of ITCs derived from GLs via the activation of myrosinase at an elevated temperature before myrosinase is deactivated (**Figure 2a**). Cooking for a longer time (>5 min) deactivates the myrosinase and prevents the
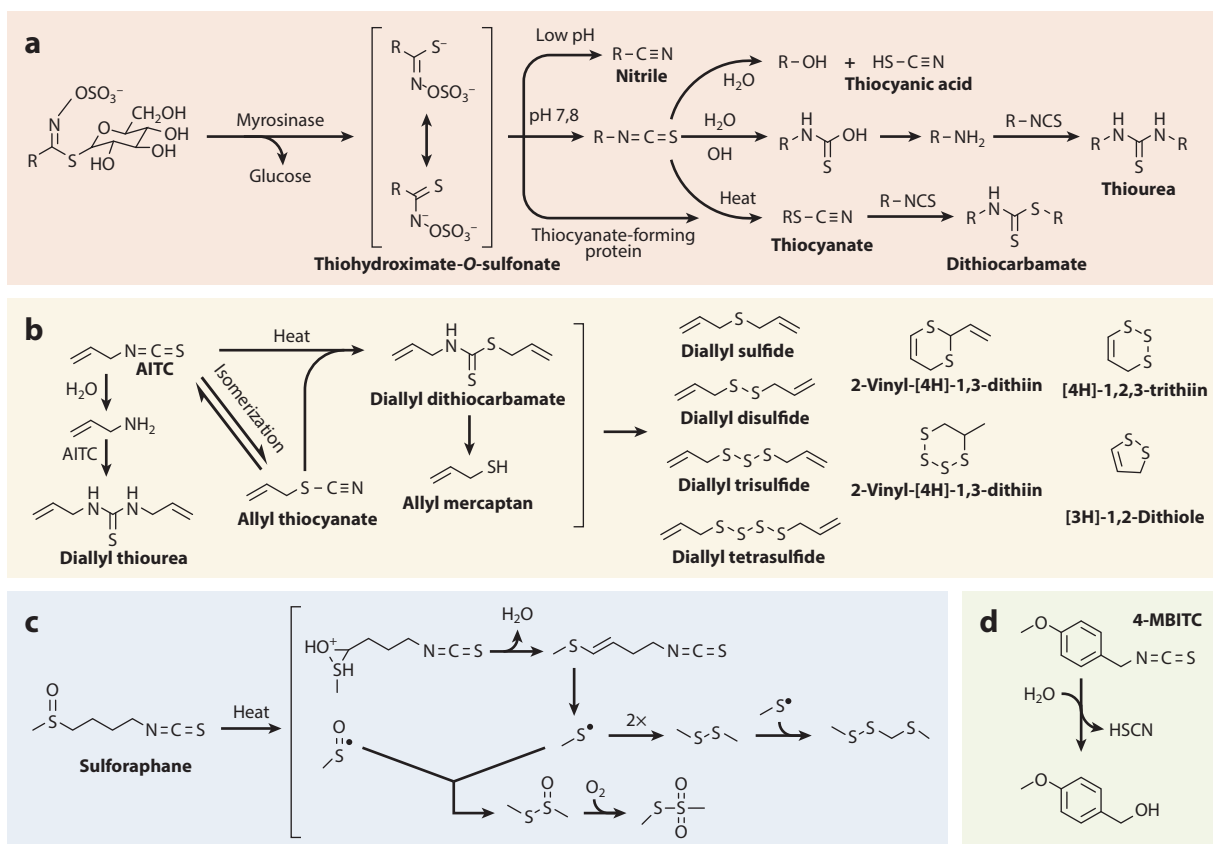
Figure 2

(*a*) Formation of isothiocyanates in cruciferous vegetables and their degradation products during thermal processing. Panel *a* adapted with permission from Lu et al. (2021). (*b*) Transformations of allyl isothiocyanate (AITC) to polysulfides during thermal processing. (*c*) Transformations of sulforaphane during thermal processing. (*d*) Transformations of 4-methoxybenzyl isothiocyanate (4-MBITC) during thermal processing. Panels *b*, *c*, and *d* were adapted with permission from Hanschen et al. (2014).

formation of ITCs but leads to thermal degradation of ITCs into thiols, sulfides, dithiin, dithiole, dithiocarbamates, and thiourea (**Figure 2b–d**).

The loss of ITCs during cooking is affected by not only the thermal-processing conditions (time and temperature) but also the varietal characteristics of the raw materials (Kapusta-Duch et al. 2016). It has been reported that cooking reduces ITC levels by 11–42.4% in cooked green and purple cauliflower compared with their respective raw vegetables (Kapusta-Duch et al. 2016). Counterintuitively, the ITC concentration increased 300% in cooked rutabaga, likely because of an initial stage of high enzymatic activity. The level of ITCs increased in steamed cabbage, and other protein factors such as epithiospecific protein (ESP) played a significant role, because of potential blocking of the rearrangement of thiohydroximate-*O*-sulfonate into ITCs. With longer cooking times, ESP is denatured and therefore the production of ITCs increases (Oliviero et al. 2018b).

Different steaming times affected the formation of SFN, which has significantly higher concentrations in raw broccoli steamed for a short time (e.g., 1 min) than in broccoli steamed for a longer time (2–3 min) (Sarvan et al. 2017). In another case, drying of Cook's Scurvy Grass (*Lepidium oleraceum*) at 45°C yielded a greater amount of 3-butenyl ITC than did drying at 75°C because the higher drying temperature inactivated the myrosinase and therefore less ITC was generated (Sansom et al. 2015). An elevated temperature of no more than 50°C may lead to stronger activity of enzymes and higher-temperature (>80°C) cooking denatures the myrosinase and suppresses the enrichment of ITCs. Furthermore, high temperatures result in decomposition of the ITC side reactions. The profile of ITC-degraded products was also affected by the pH values of the media (**Figure 2a**) (Hanschen et al. 2014, Kapusta-Duch et al. 2016). Thiocyanate was the main product in neutral and acidic conditions, whereas thiourea was the main product in alkaline conditions.

As mild electrophiles, ITCs form adducts by rapidly reacting with some nucleophiles in the food matrix or in vivo, particularly amino acids (e.g., cysteine) (Abbaoui et al. 2018, Lin et al. 2019, Lu et al. 2020). Lin et al. (2019) and Lu et al. (2020) have previously reported that the adducts of ITCs and cysteine underwent intramolecular cyclization followed by slowly releasing raphanusamic acid/organic amine and 2-carbylamino-4,5-dihydrothiazole-4-carboxylic acids (DCAs)/hydrogen sulfide (H_2S). Therefore, for ITCs to be bioavailable, consumption with vegetables and other foods may not be ideal; instead, supplements with a controlled release may be a good choice to improve ITC bioavailability. ITC-rich vegetables are suggested to be consumed as salad, provided the taste can be accepted or masked.

3.4. Transformation of Dietary Organosulfur-Containing Compounds in Shiitake Mushrooms and Truffles

Dry shiitake mushrooms are popularly used in Asian cuisine (Qin et al. 2020). Drying enhances the nutritional value, as it promotes the production of vitamin D and 5′-guanosine monophosphate (Qi et al. 2014). In addition, drying plays a crucial role in improving the flavors by forming certain volatile DOSCs not found in fresh mushrooms (Qin et al. 2020). Drying converts 3-(methylthio)propanal in fresh shiitake to other sulfides, particularly 1,2,4,5-tetrathiane, which contributes to a burned and sulfury odor with strong aroma activity (Schmidberger & Schieberle 2020). Sulfur compounds, such as DMTS, thioanisole, and 2,3,5-trithiahexane, and cyclic sulfur compounds especially lenthionine increased in the early stage of drying (0.5–1.5 h). Among these sulfur compounds, DMTS (fresh onion odor) showed the highest amount, followed by thioanisole and 2,3,5-trithiahexane (garlic-like flavor) (Qin et al. 2020). With the extension of drying time (2.5–12 h), levels of open-chain sulfuric compounds such as 2-(methylthio)ethanol, methyl allyl disulfide, dimethyl pentasulfide, and DMTS declined sharply. They may evaporate or be
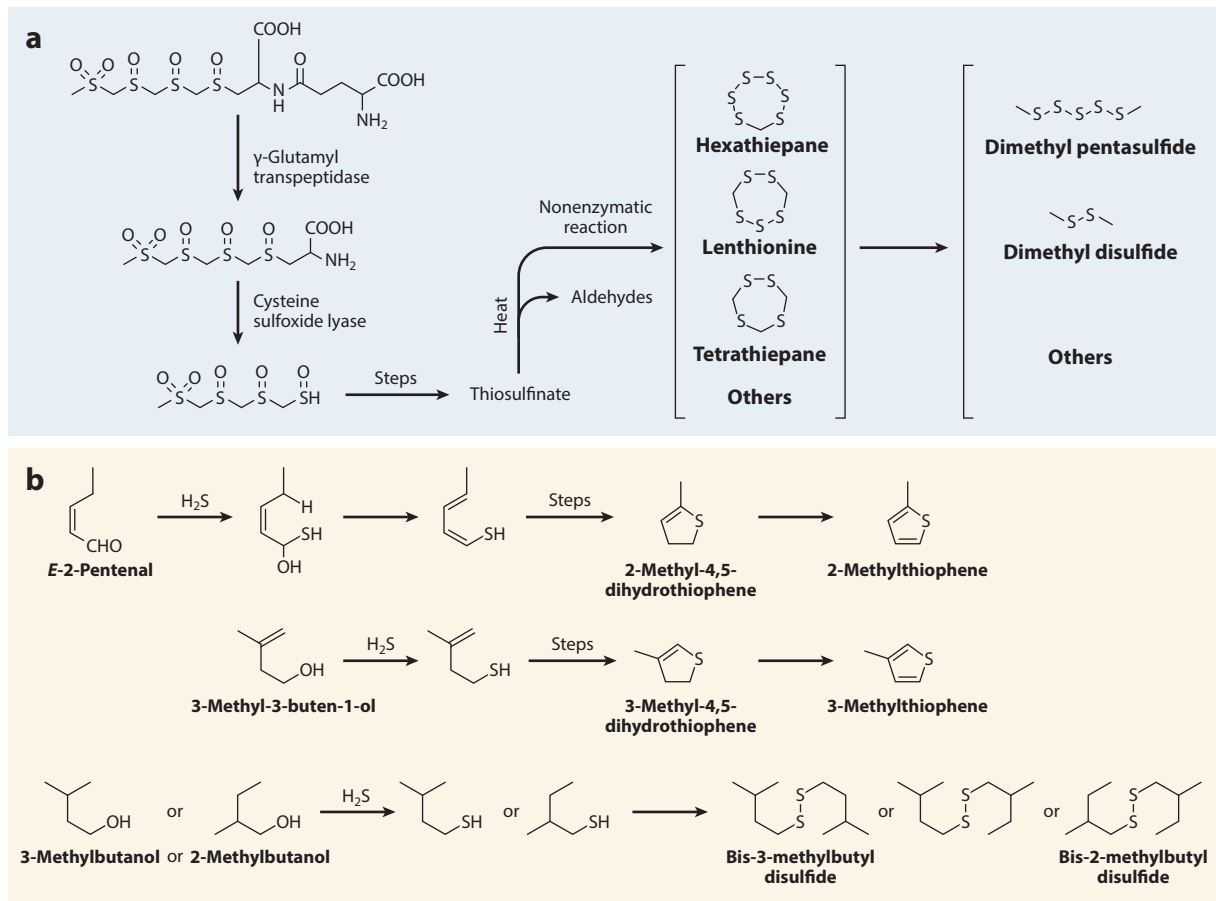
Figure 3

(*a*) Transformations of lenthionine in shiitake mushroom during thermal processing. Panel *a* adapted with permission from Qin et al. (2020). (*b*) Transformations of dietary organosulfur-containing compounds in truffle during storage. Panel *b* adapted with permission from Bellesia et al. (2001).

transformed into cyclic sulfur compounds (e.g., lenthionine) (Hiraide et al. 2004, Wu & Wang 2000), which increased gradually during the entire drying process. In general, lenthionine is produced from lentinic acid by nonenzymatic polymerization and the actions of γ-glutamyl transpeptidase (γ-GTP) and cysteine sulfoxide lyase (Qin et al. 2020). In addition, these cyclic sulfur compounds may be further degraded to sulfides and thioether compounds (**Figure 3*a***). Interestingly, when dried mushroom was rehydrated, the concentration of 1,2,4-trithiolane significantly increased, and 1,2,4,5-tetrathiane and 1,2,3,5,6-pentathiepane were newly formed (Schmidberger & Schieberle 2020).

With the growing awareness of truffles in recent years, many new truffle cuisines (e.g., stir-fried/sautéed truffles added to hot-pots with meats and vegetables) have been developed. However, few studies have reported the changes of DOSCs in truffles during cooking. The storage conditions (e.g., packaging material, storage time, and temperature) significantly affect the profiles and concentrations of DOSCs in truffles (Bellesia et al. 2001, Pennazza et al. 2013). The levels of 2,4-dithiapentane decrease gradually during storage (Aprea et al. 2007) and remain significantly

higher in blotting paper at 8°C than that found in rice (truffles were covered by rice) regardless of temperature (4°C and 8°C) after 7 days of storage (Pennazza et al. 2013). In addition, 2- and 3-methylthiophene are the two sulfur compounds in fresh truffle, and they are relatively stable during storage at 0°C, whereas many other new volatile sulfur compounds (VSCs) (e.g., bis-3-methylbutyl disulfide, 2-methyl-4,5-dihydrothiophene, and 3-methyl-4,5-dihydrothiophene) are gradually produced during storage for 12 days at 25°C.

2-Methyl-4,5-dihydrothiophene can be derived from E-2-pentenal via cyclization of its adduct with H_2S, whereas 3-methyl-4,5-dihydrothiophene can be generated from 3-methyl-3-buten-l-ol via a similar reaction mechanism (**Figure 3b**). The two compounds could be the intermediates for 2- and 3-methylthiophenes in fresh truffles. Bis-3-methylbutyl disulfide and its isomers might be formed from 3-methylbutanol or 2-methylbutanol by unknown mechanisms (**Figure 3b**). Interestingly, these compounds were abundantly released at low temperatures (e.g., 0°C) (Bellesia et al. 2001). The generation of these sulfur compounds at 25°C indicates a high amount of H_2S is released in truffles, presumably via degradation of sulfur-containing amino acids (Bellesia et al. 2001). The mechanisms of H_2S generation in truffles warrant further investigation.
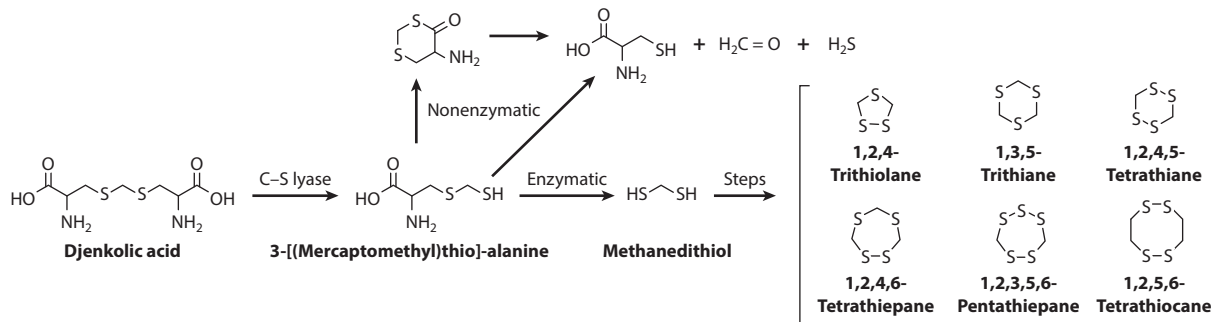
3.5. Transformation of Dietary Organosulfur-Containing Compounds in Stinky Beans and Djenkol Beans

Raw *Parkia speciosa* and *Archidendron pauciflorum* contain large amounts of djenkolic acid, which has poor water solubility. Overconsumption of foods containing high levels of djenkolic acid may cause kidney injury because of the crystallization of djenkolic acid (also known as djenkolism) (Areekul 1979, Bunawan et al. 2014). Djenkolic acid was first detected in the urine of natives of Java who included the djenkol bean in their diet (Van Veen & Hyman 1933). Soaking the beans in water or cooking the beans may reduce the djenkolic acid. Stinky bean contains relatively lower levels of djenkolic acid and can be eaten raw in small amounts or pickled, boiled, or roasted before consumption (Chhikara et al. 2018). In Thailand, stinky beans are normally served with Nam Prik mixed with spicy paste. In Malaysia, the raw or boiled stinky beans are consumed with chilies mixed with prawn paste or other seafood or boiled in coconut milk with other vegetables. In addition, the pickled matured seeds in brine are also quite popular in Malaysia (Izzah Ahmad et al. 2019).

A few studies reported the organosulfur profiles and the changes of these sulfur-containing compounds after domestic processing (How & Siow 2020). In mature stinky bean, the odorless djenkolic acid was converted to volatile and strong-smelling organosulfides (Ramírez & Whitaker 1999). Linear polysulfides such as 1,3-dithiabutane, 2,4-dithiapentane, 2,3,5-trithiahexane, and 2,4,6-trithiaheptane were detected in cooked but not in raw stinky beans (Frerot et al. 2008). In addition, boiling significantly increased the levels of thiazolidine-4-carboxylic acid (a thioproline), which is produced from the djenkolic acid found in stinky beans (Dann & Gates 1957, Suvachittanont et al. 1996).

Different extraction methods may significantly affect the analytical results for organosulfur profiles and levels of stinky bean extracts. For example, significantly more total organosulfur compounds were obtained from solvent extraction than from distillation. In addition, the pH of the food matrix significantly affected the levels of organosulfur compounds, with the highest amount at pH 5.4; lower or higher pH values decreased their levels (Tocmo et al. 2016). It is likely that these conditions alter the reaction conversion of djenkolic acid or other organosulfide precursors.

It was originally believed that djenkolic acid and dichrostachinic acid were first degraded into methanedithiol via the action of endogenous C-S lyase (plus reductase in the case of dichrostachinic acid) during the ripening of stinky beans. Other pyridoxal 5′-phosphate-containing lyases

Figure 4

Transformations of dietary organosulfur-containing compounds in stinky beans. Figure adapted with permission from Tocmo et al. (2016).

(e.g., cystathionine γ-lyase, S-alkylcysteine α, β-lyase, and cystathionase) can catalyze the α-/β-elimination of djenkolic acid to produce methanedithiol, pyruvate, and ammonia (Kamitani et al. 1991). The decomposition of djenkolic acid by C-S lyase can be postulated to proceed with the formation of a covalent Schiff base of the pyridoxal-P with the cysteine moieties of djenkolic acid. This aldimine structure as an intermediate is followed by β-elimination of methanedithiol and an enzyme-bound Schiff base of aminoacrylate. The latter spontaneously hydrolyzes into pyruvate and ammonia, thereby restoring the aldimine structure and the original state of the enzyme ready for the next reaction cycle (Greenberg et al. 1964). However, there is no direct evidence of the presence of methanedithiol during these enzymatic reactions because this compound is highly reactive and generally undergoes self-condensation and oxidation to produce a variety of polysulfides, especially in high-temperature conditions (Cairns et al. 1952). It has been suggested that the polysulfides may convert to different cyclic organosulfides as the final states of the DOSCs in stinky bean (**Figure 4**).

3.6. Transformation of Dietary Organosulfur-Containing Compounds in Durian

Owing to a short fruiting season and shelf life, durian is normally consumed fresh. Because of transportation, large amounts of durian are wasted before reaching the consumer. As a way to reduce wastage, durian is often fermented into durian alcoholic beverages and durian probiotic beverages. After fermentation with *Saccharomyces* (Lee et al. 2012, 2013; Lu et al. 2015), non-*Saccharomyces* yeasts (Lee et al. 2012; Lu et al. 2016, 2017b), and/or bacteria (Lu et al. 2017a, 2018b), VSCs (thiols and sulfides) in durian decrease to trace or undetectable levels. In addition, the changes in VSC levels at different temperatures (20°C and 30°C) and pHs (3.1 and 3.9) in durian wine fermented with *S. cerevisiae* EC-1118 were evaluated, and it was found that VSCs were more affected by temperature than pH. VSC levels decreased faster at higher temperatures regardless of pH (Lu et al. 2017c). Furthermore, compared to the bacteria monoculture (*Lactobacillus casei* L26) fermentation, the VSC levels were lowered by 20–30% and this was retained in the sequential coculture (*L. casei* L26 and *Williopsis saturnus*) fermentation, indicating the addition of yeast further lowered VSC levels (Lu et al. 2018b).

The reduction of volatile thiols could be ascribed to their oxidation to disulfides (Kreitman et al. 2016a, 2016b), the formation of nonvolatile thiols via reactions with polymeric phenolic compounds (Nikolantonaki et al. 2010), or the generation of thiol-substituted hydroquinones through reacting with *o*-quinones (Bassil et al. 2005). In addition, the volatile thiols could also be removed by mannoproteins in yeast cell walls, in which the cysteine residues reacted with free thiols and

formed disulfides (Lu et al. 2018a, Pérez-Serradilla & de Castro 2008). The decrease of sulfides (disulfides and trisulfides) might be ascribed to their reduction to corresponding thiols by yeast or bacteria under anaerobic conditions. These organosulfur compounds might also be utilized by yeasts to produce H_2S, which is an intermediate in the biosynthesis of sulfur-containing amino compounds required for cell growth and function (Gómez-Plaza & Cano-López 2011); however, this remains to be confirmed.

4. HEALTH-PROMOTION ACTIVITIES OF DIETARY ORGANOSULFUR-CONTAINING COMPOUNDS AND THEIR POTENTIAL MECHANISMS

DOSCs are credited to be the bioactive compounds responsible for the health benefits of the respective vegetables. For instance, garlic and its supplements have been believed to reduce the risk of cardiovascular disease, cancer, and age-related diseases (Kim et al. 2016b). The consumption of various ITCs (e.g., glucoraphanin, SFN, and PEITC) resulted in the increased urinary excretion of mercapturic acid metabolites of benzene, which indicated that there was increased detoxification of the polycyclic aromatic hydrocarbons (Zhang et al. 2018). It is reasonable that these compounds may have different bioactivities due to their different chemical structures and reactivity with biological targets, but it is highly challenging to pinpoint the actual action pathways for the DOSCs, partially because they are prone to be transformed into different metabolites in the GI tract and liver.

4.1. Bioavailability of Dietary Organosulfur-Containing Compounds in Digestion

Few studies have investigated the bioavailability of DOSCs because it is difficult to directly determine them in biological samples, as most of these compounds are metabolized after ingestion. In addition, they can react with the food matrix, particularly proteins and amino acids (cysteine). Nonetheless, a few papers have attempted to tackle this challenge by measuring selected metabolites as indicators of bioavailability.

Allicin is believed to be responsible for most of the bioactive properties of crushed raw garlic cloves. In a mice model, allicin was quickly metabolized in the GI tract and had an oral bioavailability of only 31%. The main metabolites were characterized to include hydroxylated allicin derivatives (Kodera et al. 2002). However, in a human, allyl methyl sulfide was identified as the main metabolite of allicin and allicin derivatives (Lawson & Wang 2005). Recently, the allicin bioavailability and bioequivalence were compared after oral ingestion of different garlic supplements (13 samples) and garlic-containing foods (9 samples) in 13 subjects (Lawson & Hunsaker 2018). Allicin bioavailability or bioequivalence varied from 36% to 104% for enteric tablets, and this value reduced to 22–57% when consumed with a high-protein meal, which could readily react with allicin. Nonenteric tablets showed higher allicin bioavailability and bioequivalence (80–111%) independent of meal types. In addition, cooked and acidified garlic foods also showed higher allicin bioavailability and bioequivalence than expected. Overall, these findings proposed a new potential way of producing garlic products to enhance allicin bioavailability. Allicin is known to react with GSH or cysteine to generate S-allylmercaptoglutathione (GSSA) or S-allylmercaptocysteine, respectively (Zhang & Parkin 2013). GSSA may be reduced by GSH reductase to generate GSH and allylthiol, which could react with other biological molecules (Horn et al. 2018).

Recently, several studies reported the pharmacokinetics of S-allyl-cysteine (SAC) in rats and dogs (Amano et al. 2015, 2016; Lee et al. 2015; Park et al. 2017). SAC was quickly and completely absorbed in the GI tract with a bioavailability of over 90% and then extensively reabsorbed in the kidneys. The main metabolites of SAC in urine were N-acetyl-(S)-allyl-L-cysteine sulfoxide (11%) and N-acetyl-(S)-allyl-L-cysteine (80%) (Amano et al. 2016).

Upon absorption, ITCs rapidly undergo electrophilic addition with GSH to form conjugates, which undergo further conversion to finally give rise to an adduct with N-acetylcysteine (Zhang 2010), which is used as a biomarker for measuring the bioavailability of ITCs. In mice and/or rat models, allyl ITC (AITC) is quickly and completely absorbed in the intestine and mainly excreted via urine (80% of administered dose), with small amounts excreted in the feces (4–9% for mice and 3–12% for rats) (Ioannou et al. 1984). However, 1-methylbutyl ITC and n-decyl ITC showed only 53.9% and 10.8% recovery rates, respectively, in the urine (Munday et al. 2006).

The potential health benefits of ITCs can be compromised by relatively lower or limited bioavailability. Food processing (e.g., cooking, drying) might be one of the factors affecting bioavailability of ITCs. In human studies, decreased bioavailability was found in cooked broccoli compared to raw broccoli (Vermeulen et al. 2008) and lower bioavailability was also reported in dried broccoli sprout powder versus fresh sprouts (Cramer et al. 2012). In addition, dietary components also affect the bioavailability of ITCs. A recent study investigated the differences in ITC bioavailability in broccoli sprouts mixed with protein, fibers, and lipid gels and reported that food structure and composition significantly modulated their bioavailability (Oliviero et al. 2018a). pH can be another factor that affects the bioavailability of ITCs because it significantly affects the degradation of GLs, the precursors of ITCs. In general, the bioavailability of ITCs closely relates to the amount of GL hydrolyzed, i.e., the more GL ingested, the greater the number of corresponding ITCs. The majority of ingested GLs (88–97%) are degraded at pH 3.6–9.1, whereas at pH 1.5, only 60% of GLs were degraded (Jing et al. 2012). It has been reported that only 69% of the GLs in cauliflower were reduced in the stomach (pH 2.0); this could be because the myrosinase in the plant tissue has been denatured at acidic conditions (Sørensen et al. 2016). Therefore, further studies should be conducted to develop products with improved ITC bioavailability.

4.2. Dietary Organosulfur-Containing Compounds as Slow Dietary Hydrogen Sulfide Donors for Cardiovascular Health Promotion

DOSCs are most well-known for their activity in promoting cardiovascular health. DOSCs have been found to modulate blood pressure, total cholesterol, and reactive oxygen species (ROS) (Shang et al. 2019, Tocmo et al. 2015). However, much work remains to be done to identify the specific active compounds among the complex mixture of DOSCs in the food matrix. Allicin was credited to be responsible for garlic supplements' ability to lower cholesterol levels but well-designed clinical trials showed that it has no positive effects (Gardner et al. 2007). The complexity of the DOSCs from different food sources seems to be able to converge to similar health benefits, suggesting that there might be a common action mechanism, and H_2S donation was suggested to be one possibility (Maslin 2008). In recent years, emerging evidence revealed the functional properties of H_2S as a vascular cell signaling molecule in cardiovascular protection (**Figure 5**). The production of H_2S from the biological transformation of DOSCs is related to cardiovascular benefits, including relaxation of vascular smooth muscle, reduction of systolic blood pressure, and cardio-protection during myocardial ischemia and acute myocardial infarction (Chhikara et al. 2018, Hsu & Tain 2021).

There are a few pathways that generate H_2S from DOSCs. DADS and DATS could be converted to H_2S both in vitro and in vivo via reaction with GSH (**Figure 5a**) (Benavides et al. 2007,
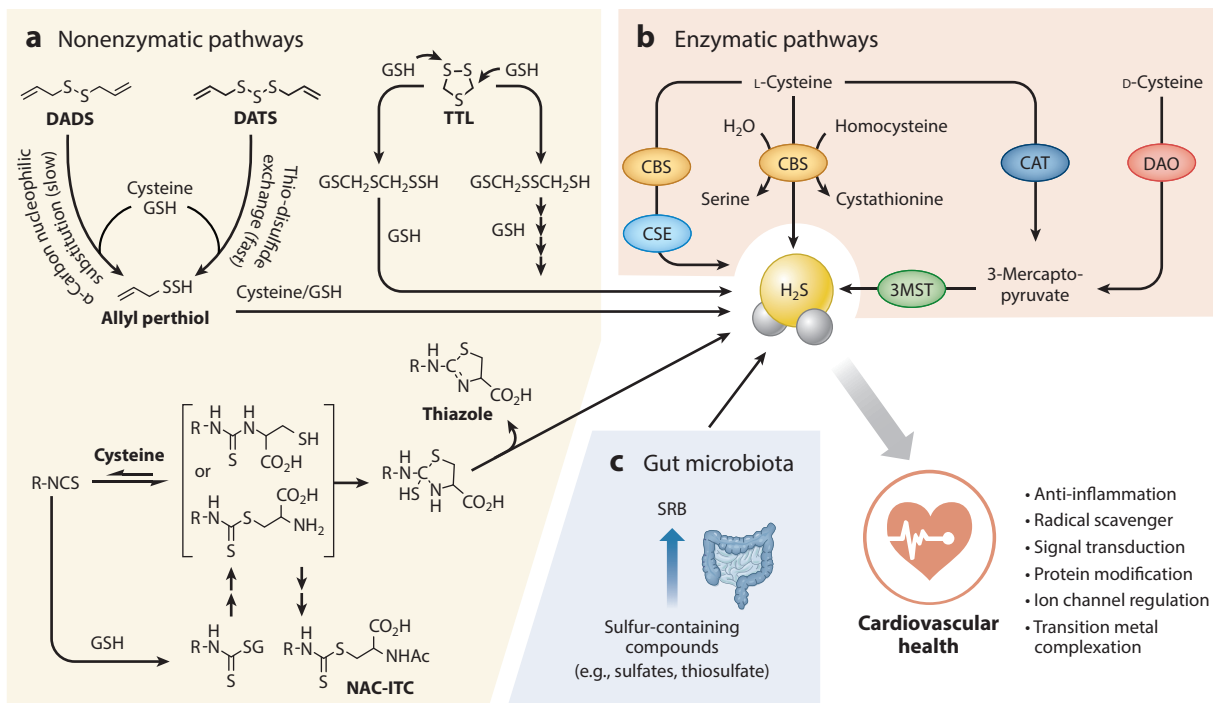
Figure 5

H_2S formation pathways, including (*a*) nonenzymatic pathways (polysulfides, TTL, ITCs). Panel *a* adapted with permission from Liang et al. (2015b, 2017), Lin et al. (2019), and Lu et al. (2020). (*b*) Enzymatic pathways (in vivo homocysteine, D-cysteine). (*c*) Gut microbiota (sulfate, and thiosulfate). Panels *b* and *c* adapted with permission from Hsu & Tain (2021). Abbreviations: 3MST, 3-mercaptopyruvate sulfurtransferase; CAT, cysteine aminotransferase; CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; DADS, diallyl disulfide; DAO, D-amino acid oxidase; DATS, diallyl trisulfide; GSH, glutathione; ITC, isothiocyanate; NAC, *N*-acetylcysteine; R-NCS, various isothiocyanates; SRB, sulfur-reducing bacteria; TTL, 1,2,4-trithiolane.

Liang et al. 2015b, Tocmo et al. 2017b). Benavides et al. (2007) reported that DADS produces H_2S via an α-carbon nucleophilic substitution pathway with allyl perthiol as a key intermediate. Although a recent study (Liang et al. 2015b) found that DADS produced only a small amount of H_2S through a sluggish (over a few hours) reaction with GSH, the rapid H_2S releasing phenomenon could be attributed to its DATS impurity (Benavides et al. 2007, Liang et al. 2015b). The DATS impurity reacts rapidly (within minutes) with GSH and the H_2S is released via a thiol-disulfide exchange and/or allyl perthiol reduction by GSH (**Figure 5a**).

In addition, Liang et al. (2015a) evaluated the H_2S-releasing capacity of essential oils from some organosulfur-rich vegetables and fruits (e.g., garlic, onions, scallion, shallot, leek, Chinese chives, durian, and stinky beans) and found that stinky beans exhibited a very high H_2S-releasing capacity. Stinky beans are rich in cyclic polysulfides, which may be slowly (hours) converted into H_2S in a more efficient way than linear polysulfides in other vegetables (Liang et al. 2015a, Tocmo et al. 2016). Liang and colleagues (2017) further purified 1,2,4-trithiolane, the major cyclic polysulfide in stinky beans, and found that it is a potent but slow H_2S donor (**Figure 5a**). It was 6.35 times more effective in releasing H_2S than was DATS.

Natural ITCs from cruciferous vegetables have also been reported as H_2S donors. Citi et al. (2014) reported for the first time the H_2S-releasing capacity of several natural ITCs (e.g., AITC,

BITC) by amperometric detection of H_2S. In addition, X. Wang et al. (2018) evaluated the H_2S-releasing capacity of moringa tissues (e.g., seeds, roots, leaves, and stems) by a lead (II) acetate paper method and found that it showed a positive correlation with ITC levels. The H_2S-releasing mechanisms of ITCs have been further elucidated (Lin et al. 2019, Lu et al. 2020) to find that ITCs rapidly reacted with L-cysteine to form adducts, which underwent slow intramolecular cyclization and then released raphanusamic acid/organic amine and DCAs/H_2S (**Figure 5a**). In addition, Lu et al. (2020) found that the R groups of ITCs (R-NCS) significantly affected their H_2S-releasing capacity and rates. For example, 4-hydroxybenzyl ITC (HBITC) showed a fast H_2S-releasing rate but an extremely low H_2S-releasing capacity, whereas a synthetic ITC, 4-nitrophenyl isothiocyanate (NO$_2$PITC) showed both the highest H_2S releasing rate and capacity among six measured ITCs (PEITC, BITC, PITC, p-methoxyphenyl isothiocyanate, p-chlorophenyl isothiocyanate, and NO$_2$PITC) (Lin et al. 2019). Except for the functional roles of H_2S, Lu et al. (2020) also hypothesize that the main products from the reactions of ITCs and L-cysteine, DCAs, may play some biological beneficial effects. However, these DCAs did not exhibit anticancer and anti-inflammatory activity even at very high concentrations (Lu et al. 2020). This indicated that the -NCS group of ITCs (R-NCS) is necessary for their cancer chemoprevention activity.

Along with DOSCs and endogenous H_2S generation by enzymes, the metabolism of gut microbiota (e.g., sulfur-reducing bacteria) may act on sulfates and thiosulfate to generate H_2S. It is likely the organopolysulfides could be reduced to also generate H_2S in the reducing environment in the gut (**Figure 5c**).

The evidence so far has shown that three classes of DOSCs (ITCs, polysulfides in garlic, and cyclic sulfides in mushroom and stinky beans) can all lead to the formation of H_2S in chemical and cellular conditions. Future work should focus on in vivo and human clinical trials using markers that are specific to those of H_2S activity to assess how significant this mechanism is in the health-promotion activity of DOSCs.

4.3. Action Mechanisms of Dietary Organosulfur-Containing Compounds for Cancer Chemoprevention

H_2S has been shown to have anticancer activity (Li et al. 2020). Thus, it could be an important ingredient in the mechanism that allows DOSCs to act as cancer chemoprevention agents. Organosulfur compounds from natural products such as onion, garlic, cruciferous vegetables, and *Moringa oleifera* have been reported to protect against diverse cancers (e.g., prostate, lung, breast, oral, gastric cancers) via various mechanisms, which mainly include (*a*) regulation of the metabolism of carcinogenic substances, (*b*) suppression of cell growth and proliferation, (*c*) induction of apoptosis, (*d*) inhibition of invasion and migration, and (*e*) suppression of angiogenesis (**Figure 6a**) (Nicastro et al. 2015, Shang et al. 2019). Herein, we examine the different pathways the DOSCs may interfere with to slow down cancer development that may or may not involve H_2S.

4.3.1. Suppressing procarcinogen activation.

DOSCs from alliums can help reduce the risk of cancer via mitigating the activation of carcinogens (Smith et al. 2016). For example, allyl sulfides (ASs) from garlic can inhibit the production of some carcinogens such as nitrosamines, which are normally formed during cooking and storage (Shang et al. 2019). In addition, ASs can also block DNA alkylation to reduce the risk of nitrosamine carcinogenesis (Nicastro et al. 2015). ITCs were known to reduce the activity of phase I enzymes (P450) while upregulating the expression of phase II enzymes, thus increasing detoxification speed and reducing the formation rate of carcinogens, which prevent the initiation of DNA damage, the first step of cancer formation.
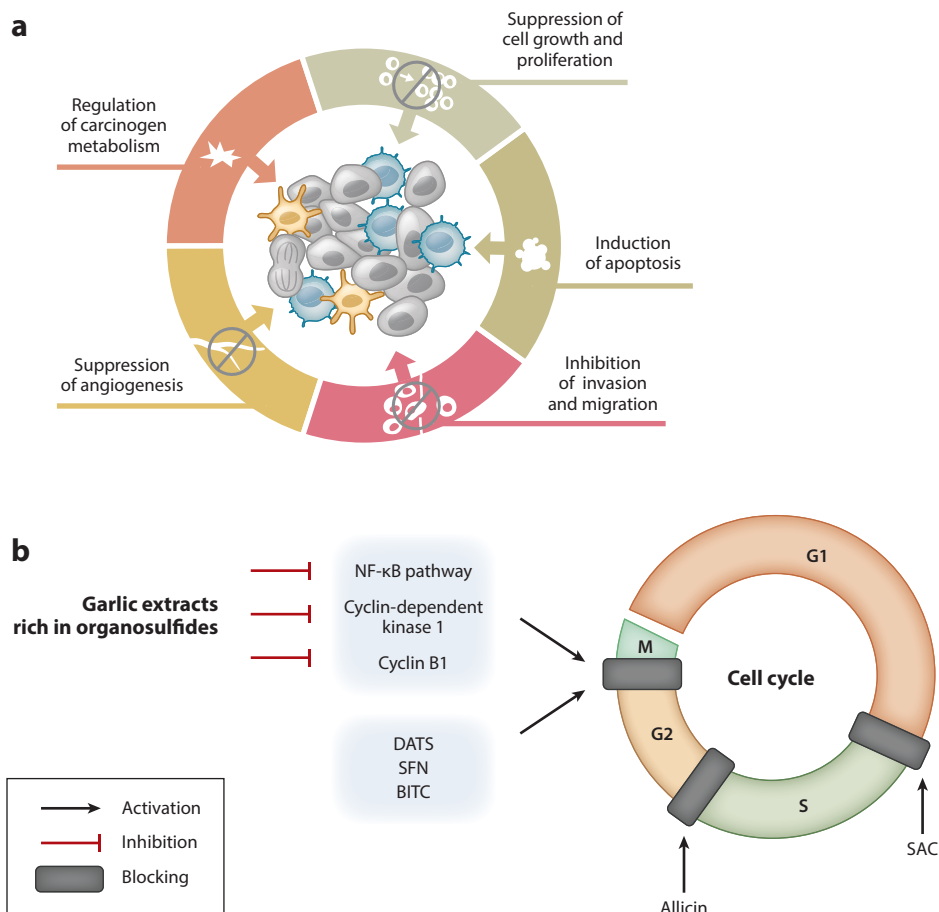
Figure 6

(*a*) Potential targets of dietary organosulfur-containing compounds (DOSCs) for cancer chemoprevention. Panel *a* adapted with permission from Hanahan & Weinberg (2011) and Shang et al. (2019). (*b*) Anticancer mechanisms of DOSCs (from the inhibition of the cell cycle in cancer cells). Panel *b* adapted with permission from Shang et al. (2019). Abbreviations: BITC, benzyl isothiocyanate; DATS, diallyl trisulfide; G1, cell cycle gap 1 phase (cell growth, preparation for DNA synthesis); S, cell cycle S phase (DNA synthesis); G2, cell cycle gap 2 phase (cell growth, preparation for mitosis); M, cell cycle mitosis phase; NF-κB, nuclear factor κB; SAC, S-allyl-cysteine; SFN, sulforaphane.

4.3.2. Suppression of cell growth and proliferation. DOSCs from alliums and/or cruciferous vegetables exhibited antiproliferative effects on various human cancer cell lines such as MCF-7 (breast), Hep-G2 (liver), HCT-116 (colon), and PC-3 (prostate) (Bagul et al. 2015, Lu et al. 2020, Pan et al. 2018). *S*-allylmercaptocysteine (SAMC) inhibits the proliferation of hepatocellular carcinoma cells and prolongs the percentage of the G0/G1 phase while shortening the S phase (**Figure 6*b***) (Xiao et al. 2018), whereas SAC blocks the cell cycle in the G1/S phase in human epithelial ovarian cancer cells (A2780) (Xu et al. 2014). In addition, SAMC and SAC suppress the proliferation of gastric adenocarcinoma cells by blocking the cell cycle in the S phase (Mansingh et al. 2018). Although DATS diminishes the proliferation of gastric cancer cells (SGC-7901) and induces cell cycle arrest in the G2/M phase via upregulating the expressions of cyclin A2 and cyclin B1 (Jiang et al. 2017).

SFN inhibits the growth and proliferation of breast cancer cells (SKBR-3 and MDA-MB-231) by inducing G2/M cell cycle arrest and changing the cytoskeletal organization (Pawlik et al. 2017). Similarly, BITC inhibits human oral OSCC cancer cell growth and induces G2/M phase cell cycle arrest (**Figure 6b**) (Yeh et al. 2016). BITC can also inhibit the growth of lung cancer cells (A549, H661, SK-MES-1) by inducing cell autophagy via activating endoplasmic reticulum stress (Zhang et al. 2017).

4.3.3. Induction of apoptosis. Some DOSCs have been found to induce apoptosis via modulating the expression of apoptotic-related genes. For example, SAMC caused apoptosis of SW620 human colorectal carcinoma cells via interfering with p38 mitogen-activated protein kinase (p38 MAPK) and Jun N-terminal kinase (JNK) pathways (Zhang et al. 2014). SAC induced apoptosis via (*a*) decreasing the expression of Bcl-2, poly(ADP-ribose) polymerase-1 (PARP-1), and procaspase-3 and (*b*) increasing the accumulation of Bax protein and the expression of active caspase-3 (Xu et al. 2014). In addition, alliin was found to induce the production of ROS, which resulted in the apoptosis of gastric adenocarcinoma cells (Mansingh et al. 2018). Furthermore, DATS increased the expression of cytochrome c, bax, and p53, which resulted in more apoptosis of SGC-7901 gastric cancer cells (Jiang et al. 2017).

Certain DOSCs could induce apoptosis by reacting with biological thiols (e.g., GSH, cysteine, or cysteine residues) via *S*-thiolation or disulfide exchange. It has been reported that ajoene can *S*-thiolate an active cysteine Cys58 to inhibit the activity of GSH reductase, whereas DATS can *S*-thiolate the two β-tubulin cysteines Cys12β and Cys354β, resulting in the induction of apoptosis in cultured human colon cancer cells (Hitchcock et al. 2021, Hosono et al. 2005).

AITC can induce apoptosis of human prostate cancer cells (RV1 and PC3) through the upregulation of beclin-1 (Chen et al. 2018). AITC showed different apoptosis mechanisms between two breast cancer cell lines, MCF-7 (estrogen receptor positive) and MDA-MB-231 (estrogen receptor negative) cells. It induced MCF-7 cell apoptosis via the apoptosis-inducing factor and endonuclease G signaling pathways and induced MDA-MB-231 cell apoptosis through the growth arrest– and DNA damage–inducible gene 153 (GADD 153) pathway (Bo et al. 2016). In addition, AITC inhibited cancer cell proliferation and induced cell apoptosis through enhancing caspase-3 and caspase-9 activity in the protein kinase B (PKB; also known as AKT) mammalian target of rapamycin (mTOR) pathway (Chang et al. 2021). BITC was able to trigger cancer cell apoptosis through the production of ROS and nitric oxide (NO), which causes DNA damage while changing the redox balance (Yeh et al. 2016), and it induced breast cancer cell apoptosis via inhibition of mitochondrial fusion under the action of Bak protein (Sehrawat et al. 2016). Moreover, BITC induced apoptosis through cell shrinkage and DNA fragmentation, likely via a mitochondria-dependent pathway (Lee et al. 2018).

4.3.4. Inhibition of cancer cell invasion and migration. All cancer cells possess malignant behaviors such as migration and invasion (Hanahan & Weinberg 2011). It has been reported that SAC inhibited the migration of cancer cells (human epithelial ovarian A2780) in vitro by decreasing the accumulation of c-Jun proteins, phosphor-protein kinase B, and wingless-type MMTV integration site family member 5A (Wnt5a) (Xu et al. 2014). In addition, ajoene inhibited the invasion and migration of MDA-MB-231 breast cancer cells in vitro via *S*-thiolating its vimentin at Cys328 (Hitchcock et al. 2021, Kaschula et al. 2019). Furthermore, DATS modulated the expression of MMP9 and *E*-cadherin protein to attenuate the migration and invasion of gastric cancer cells (SGC-7901) in vivo (BALB/c-nude mice) (Jiang et al. 2017).

ITCs also exhibited the ability to inhibit invasion and migration in in vitro studies. For example, BITC inhibits breast cancer cell migration via inhibiting AKT (Roy et al. 2019), and PEITC

suppresses the prostate cancer cell invasion and migration via reducing the expression of various oncogenic matrix metalloproteinases (Zhang et al. 2016).

4.3.5. Suppression of angiogenesis. Only a few studies have investigated the effects of DOSCs on angiogenesis. DATS was reported to effectively prevent in vitro angiogenesis in a dose-dependent manner in human breast cancer cells (MDA-MB-231), whereas DAS and DADS did not show such an effect (Wei et al. 2017). The underlying mechanisms should be further evaluated. Although there are enough in vitro studies on DOSCs to suggest that they may act as anticancer agents, more well-designed human clinical trials are needed to establish strong evidence for their anticancer benefits.

4.4. Anti-Inflammatory Activity and Mechanisms of Dietary Organosulfur-Containing Compounds

Inflammation is believed to be the causative factor for many chronic diseases, including cancer. Inflammation is triggered by many proinflammatory pathways, which could be the targets of anti-inflammatory agents. The most well-studied inflammatory regulators are the NF-κB and nuclear factor E2-related factor 2 (Nrf2), which are two transcription factors that regulate the expressions of proinflammatory (NF-κB)/anti-inflammation (Nrf2) genes. NF-κB can be activated by proinflammatory cytokines such as such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β. Nrf2 can be activated by phytochemicals including DOSCs.

DOSCs from allium upregulated the anti-inflammatory cytokine IL-10 expression and downregulated both proinflammatory cytokines (e.g., IL-1β, IL-6, IL-12, TNFα, and IL-1α) and several chemokines (e.g., CCL2, CXCL1, CXCL8, CXCL9, and CXCL10) (Bauer et al. 2014, Hitchcock et al. 2021, Shi et al. 2017). In addition, these DOSCs also dampened or functionally modulated activities of COX and lipoxygenase (Hitchcock et al. 2021, Nicastro et al. 2015). For example, DAS, DADS, and AMS differentially modulated the production of NO, prostaglandin E_2, and cytokines in mouse macrophages induced by lipopolysaccharides (LPS) (Chang et al. 2005). Hitchcock et al. (2021) investigated the anti-inflammatory activity of allicin and ajoene using LPS-induced murine macrophage cells as a model. They found that the two garlic DOSCs upregulated the production of the anti-inflammatory cytokine IL-10 and inhibited both transcript and protein expression of the proinflammatory cytokines (e.g., IL-1β, IL-6, and IL-12β). Ajoene showed not only a pronounced downregulation toward inflammatory cytokines and chemokines but also dose-dependent and noncompetitive inhibitory activity toward COX-2; this was ascribed to *S*-thiolation at Cys9 and Cys299 in LPS-induced macrophage cells (Hitchcock et al. 2021).

ITCs, including moringin [4-(α-ʟ-rhamnopyranosyloxy)-benzyl ITC (RBITC)] (Waterman et al. 2014), PEITC (Lee et al. 2011), and SFN (Townsend & Johnson 2016), attenuated the expression of various inflammatory markers, e.g., iNOS, IL-1β, NO, and TNFα, in LPS-induced inflammatory cells. In addition, the oral administration and topical application of PITC on mouse ears helped to suppress the inflammatory responses caused by LPS (Lee et al. 2011). However, the consumption of whole broccoli in young and aged mice attenuated the expression of IL-1β but reduced cytochrome b-245β, a functional component of the NADPH oxidase system that contributes to the release of free radicals from phagocytic cells, and glial activation markers (Townsend et al. 2014). These results may indicate that the form in which the ITCs are consumed likely impacts their effectiveness, with pure supplements being more preferable.

Human clinical trials bear the weight of the evidence for health-promotion activity of DOSCs. A randomized crossover study by Navarro et al. (2014) found that the consumption of cruciferous and/or apiaceous vegetables resulted in lower levels of IL-6 (a proinflammatory cytokine in the

NF-κB inflammatory pathway), with an inverse association found between the IL-6 levels and the urinary ITC levels. However, no significant changes were reported for other inflammation markers, which may be attributed to the difference in the response of the markers to environmental factors or differences in the rate of response. The study also suggested that ITCs may affect other possible inflammatory pathways. For example, it was reported that ITCs (e.g., PEITC) were able to mediate the signaling of the NFR and PTEN/PI3K/AKT pathways (H. Wang et al. 2018).

4.5. Dietary Organosulfur-Containing Compounds as Antimicrobial Agents

Garlic has long been used as a natural antibiotic and disinfectant because of its high levels of DOSCs (Kyung 2012). These DOSCs showed broad antimicrobial activities against bacteria (both Gram-positive and Gram-negative), fungi, viruses, and parasites (Foroutan-Rad et al. 2017, Petropoulos et al. 2017). Petropoulos et al. (2017) reported that allicin exhibited higher antimicrobial activity against methicillin-resistant *Staphylococcus aureus* than some traditional antibiotics. The potential mechanism was attributed to the immediate and total inhibition of RNA synthesis (Saad & Mona 2013) and/or the combined results of decreased GSH level, unfolded stress, and inactivated crucial metabolic enzymes (Müller et al. 2016). In addition, allicin synergistically improves the antifungal activity of amphotericin B (one of the antimicrobials) via modulating the intracellular ergosterol trafficking (Ogita et al. 2009).

ITCs exhibit antimicrobial activity against bacteria (Olaimat & Holley 2016) and fungi (Tracz et al. 2018). Not surprisingly, R group in R-NCS influences the activity (Sotelo et al. 2015). The R group containing sulfonium shows a stronger inhibitory activity to oral pathogens than aromatic and aliphatic R groups. In addition, ITCs containing a sulfide bond (-S-) show more effective antimicrobial activity against bacteria (e.g., *Streptococcus mutans*, *S. aureus*) and yeast (e.g., *Candida albicans*) than ITCs containing sulfinyl (-SO-) groups. Moreover, the presence of a double bond in the side chain of ITCs decreased their antimicrobial activity. For example, SFN showed a similar structure as sulforaphene, and the latter has a C=C bond, which led to its lower antimicrobial activity. Furthermore, the antimicrobial activities of ITCs can be significantly affected by the length of the hydrocarbon chain. Li et al. (2013) reported that a short-chain BITC showed stronger antimicrobial activity than PEITC against fungi (e.g., *C. albicans*) and bacteria (e.g., *S. mutans*, *S. aureus*).

In a previous study, Lu et al. (2020) screened the antimicrobial activities of three dietary ITCs (BITC, HBITC, and RBITC) against different Gram-positive bacteria, *S. aureus*, *Staphylococcus hominis*, and *Enterococcus faecalis*, and Gram-negative bacteria, *Salmonella typhimurium*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Although the three ITCs shared similar structures, they showed different antimicrobial activities against different bacteria. BITC exhibited higher antibacterial activities against *S. hominis*, *E. faecalis*, *S. typhimurium*, and *E. coli* than did HBITC and RBITC, whereas RBITC showed the highest selective antibacterial activity against *S. aureus*, followed by BITC and HBITC (Lu et al. 2020). The different antibacterial activities of ITCs were ascribed to the differences in cell wall structures and cell membrane permeability of different bacteria (Padla et al. 2012). In addition, Olaimat & Holley (2016) reported that AITC was lethal toward *E. coli* O157:H7, *Salmonella* spp., *Listeria monocytogenes*, and *Campylobacter jejuni*. It reduced the viability of *L. monocytogenes* and aerobic bacteria on cooked, cured roast chicken slices by 4.1 $\log_{10}$ CFU/g compared to the control stored for 70 days at 4°C. Because antimicrobial activity of DOSCs was the result of direct interaction of the DOSCs with the microbes, mechanistically, it is chemically possible that the DOSCs may react with GSH and/or with thiol functional groups to increase the oxidative stress and generate H_2S, which could be toxic to the microbes via suppression of mitochondrial activity. For example, rapid H_2S donor DATS could work through this mechanism (Andreadou et al. 2020).

5. CONCLUSIONS AND PERSPECTIVES

In summary, DOSCs found in raw fruits and vegetables may all be classified as constitutive phytoalexins in the form of cysteine derivatives (alliin, isoalliin, djenkolic acid) and GLs. They may have their own bioactivity and require deactivation of the enzymes if their concentrations need to be kept at constant levels. These odorless and nonvolatile compounds are readily converted to phytoalexins such as allicin, ITCs, thiols, and polysulfides. It is not surprising that they have antimicrobial activity, as plants utilize phytoalexins for their self-defense against injury. These reactive DOSCs are all able to act as H_2S donors, which may be one of the many reasons for their health-promotion activity. The complexity of the chemistry of DOSCs arises because of their high sensitivity to food processing methods (e.g., thermal treatment or fermentation) and reactions with the food matrix, particularly proteins. As the bioactivity of the DOSCs is dependent on the specific structures of each compound, each one must be investigated individually rather than in a mixture to establish the structure and activity relationships in clinical settings. In vitro cellular and chemical models will also be necessary to advance the evidence-based functional foods of DOSCs.

DISCLOSURE STATEMENT

ACKNOWLEDGMENTS

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