Chemo-preventive Activities of Common Vegetables’ Volatile Organic Compounds (VOCs)

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Abstract
In the last few years, many research reports on the chemo-preventive activities of vegetables have been published. Vegetables are not only nutrient-dense food source but they are also rich in volatile organic compounds with known bioactivities beneficial to human health. A review of vegetables volatile constituents and their bioactivities is therefore important. It will display an overview and information regarding their role in the improvement of human health. The current status of research on volatile organic compounds in common vegetables and their potential roles in the prevention of various diseases associated with oxidative stress, such as cardiovascular and neurodegenerative diseases are reviewed. The major volatile compounds with roles in cardiovascular and neurodegenerative disease prevention are benzene propane nitrile commonly found in (Broccoli raab), hydroxycinnamates (lettuce), xanthorrhizol (artichoke), dially sulfide (onion and garlic), allicin (onion and garlic), and anthraquinone (rhubarb). The anti-microbial, anti-oxidant, and anti-thrombotic activities of other compounds such as trans-ocimene, β-selinene, fenchone, carotol, and others are also reported.

Keywords: Chemo-preventive activities; vegetables; volatile organic compounds

Practical Application
In recent years, common vegetables have become very attractive for consumers because of their potentially beneficial volatile compounds contained in them. However, the role played by volatile organic compounds in disease prevention has not received the same attention.

Introduction
Vegetables can be said to either directly or indirectly supply all foods for humans. They are edible plant products which can be modified. Their important parts are stems, roots, leaves, flowers and fruits. They are usually categorized on the basis of the plant part that is used for food. Stem vegetables include kohlrabi, celery, and asparagus. Radishes, turnips, carrots, and beets are classified as root vegetables. Leafy vegetables include the cruciferous kale, endives, and lettuce. The flowery parts of vegetables are the broccoli, cauliflower, leeks, artichoke and the Allium genera. The fruits are structures usually containing seeds which develop after fertilization or pollination [1]. Thus, eggplants, cucumbers, beans, squash, bell peppers, corn and tomatoes fall into this category.

Flavor compounds in vegetables are contained in the intact tissues as non-volatile precursors which become volatile by enzymatic actions once the tissue is disrupted by crushing, cutting or shredding. Vegetable volatiles are nitrogen and sulphur compounds, and carboxyls [2]. Vegetables are not only nutrient-dense food sources, but they are also rich sources of bioactive volatile organic compounds (VOCs). VOCs are organic compounds with high vapor pressure at room temperature. VOCs are many, ubiquitous and include naturally occurring chemicals. Most scents or odors are regarded as VOCs. Literature sources have shown that a multitude of bioactive compounds in vegetables have anticarcinogenic properties [3,4]. These nutrient-dense and bioactive volatile foods have the potential to protect against chronic and degenerative diseases including diabetes and cardiovascular diseases [5,6]. The aim of the study is to review the bioactivities of volatile organic constituents of common vegetables in human health.

Materials and Methods

Fruit part of vegetables

Bell Pepper (Capsicum annuum): Capsicum annuum also called bell pepper or sweet pepper are native plants of America, and the fruits are grown for consumption as vegetables, spices, and external medicines [7]. Capsicums are used primarily in food because of their pungency and colour [7]. Apart from capsaicinoids, a secondary metabolite of pepper, which gives pepper its pungency, other volatile constituents include trans-beta-ocimene, limonene, methyl salicylate and linalool (Table 1) [8]. Whole dried pepper fruits have been used as traditional grain protectant in West Africa [9]. Admixture of dry pepper powder and cowpea has been known to cause 46% mortality in adult C. maculates, a common pest of stored legumes. The ethanol extracts of bell pepper have been shown to cause 100% adult mortality in T. confusum after a five days exposure period. Perry, [10] reported the major constituents to be capsicine, capsacin, capsanthine, capsochrome, carotene and carotenoids respectively. Diterpenoid glycosides isolated from the fruit C. annuum exhibited anti-hypertensive effects [11,12].

Cucumber (Cucumis sativus, L.): C. sativus belongs to the same cucurbitaceae family as squash, muskmelon and watermelon. It’s a seasonal vegetable crop native to India [13]. All the parts of this plant (leaf, fruit, seed) have been explored for their therapeutic benefits. Cucumber is widely used for various skin problems and it’s believed to promote cooling, healing, soothing, emollient, and anti-itching effect on irritated skin. The leaves, stems and roots are generally used.
| Volatile compounds/phytochemicals | Possible bioactivity | Types of vegetable* | Reference |
|----------------------------------|----------------------|---------------------|-----------|
| 1 Lactones                        | Exhibits anti-microbial activity against *B. subtilis, P. vulgaris* | Celery             | Siapailene, et al. [85] |
| 2 Trans-Ocimene                   | Exhibits anti-microbial activity against *B. cereus* |                        |           |
| 3 3-Methyl-4-ethylhexane          | -ditto-              |                     |           |
| 4 β-Pinene                        | Anti-oxidative and hypolipidemic activity |                     |           |
| 5 9 (Z)-Octadecenamide            | Anti-oxidant properties | Celery             | Cheng et al., [92] |
| 6 β-Selinene                      | Possess acaricidal activity against *D. farina & D. pteronyssinus* |                        | Ou et al., [49] |
| 7 Fenchone                        | Inhibits reactive oxygen species |                        |           |
| 8 Eugenol                         | Good scavengers of peroxyl radicals |                        |           |
| 9 Carvone                         | -ditto-              |                     |           |
| 10 Xanthorrhizol (sesquiterpene)  | Neuroprotective effect against cisplatin-induced nephrotoxicity | Artichoke           | Kim et al., [25] |
| 11 Carotol                        | Antifungal, herbicidal and anti-microbial |                        | Jasicka-Misiak, et al., [43]; Glisic et al., [46] |
| 12 Daucol                          | -ditto-              |                     |           |
| 13 Undecan-2-one                  | Anti-microbial & nematocidal |                        | Ntalli et al., [45]; Dorman & Deans [47] |
| 15 Sabinene                       | Anti-microbial against *B. subtilis* |                        |           |
| 16 Anethole                       | Anti-microbial, estrogenic agent and anti-thrombotic agent. Increases milk secretion/promote menstrual flow | Carrot             | Kubo et al., [32] |
| 17 p-anisaldehyde (+)-Fenchone    | Acaricidal activity |                        |           |
| 19 Estragol                       | -ditto-              |                     | Lee, [35]; Parejo et al., 2004b |
| 20 Kaempferol-3-O-rutinoside      | Anti-radical scavenging activities |                        |           |
| 21 Hydrocycinnamates              | Neuroprotective effect such as Alzheimer’s disease |                     | Commenges et al., 2000 |
| 22 3-Butenylisothiocyanate        | Inhibits the growth of pathogenic bacteria | Lettuce             | Jang et al., [25] |
| 23 4-Pentenylethylisothiocyanate  | -ditto-              |                     |           |
| 24 Benzene propane nitrile        | Anti-carcinogenic |                        |           |
| 25 1H-Indole-3-acetonitrile       | -ditto-              |                     |           |
| 26 Lycopene                       | Anti-oxidant activity, reduction of cardiovascular disease (CVD) |                        | Kardinaal et al., 1993; Erdman et al., 2005 |
| 27 Limonene                       | Antibacterial        |                     |           |
Table 1: Some volatile constituents of common vegetables and their possible bioactivities.

|   |   |   |
|---|---|---|
| 28 | Capsidiol | Bacteriostatic properties |
| 29 | Limonene | Antibacterial |
| 30 | Trans-β-ocimene | -ditto- |
| 31 | Allicin | Anti-carcinogen, anti-mutagen and anti-oxidant |
| 32 | Dially sulphide | Inhibition of colon and oesophageal carcinomas |
| 33 | 4-Methylbutyl isothiocyanate | Anti-oxidant action |
| 34 | Phenylethyl isothiocyanate | Chemopreventive properties |
| 35 | Incensole, α-Copaene | Anti-inflammatory, Antioxidant & Anticarcinogenic |
| 37 | Anthraquinone | Laxative, antimalarial, antineoplastic & in treatment of cancers |
| 38 | Dihydroquercetin | Antioxidant activity |

as anti-diarrheal, detoxicant and anti-gonorrhoeal agents among the Chinese folks. Cucumber potentials as an antioxidant, anti-wrinkle, antimicrobial, anti-diabetic, and hypolipidemic agents have been well documented.

The presence of cucurbitacin (a triterpenoid substance) in cucumber seed has been attributed to its cytotoxicity and anti-cancer activities. Guha and Sen [14] reported that cucurbitacin also exhibited wide ranges of in-vitro and in-vivo pharmacological effects and is used as purgative, anti-inflammatory and anti-fertility agent. The volatile oils of *C. sativus* have been reported to show antibacterial activity (MIC=0.09-0.5 mg/mL) against both gram-positive and gram-negative bacteria [15], and anti-fungal activity against human pathogen fungi (*C. albicans, C. tropicalis, and C. glabrata*) [16]. Similarly, (E,Z)-2,6-nonadienal and (E)-2-nonenal, the major volatile constituents present in cucumber have been reported to show anti-bacterial activity against human and food borne pathogen bacteria, such as *Bacillus cereus, Escherichia coli, Listeria monocytooges* and *Salmonella typhiriam* [16]. Stratil et al. [17] reported that cucurbitacin D and 23,24-dihydroxycucurbitacin D, isolated from cucumber extracts significantly inhibited tyrosinase and melanin synthesis.
Root part of vegetables

Onions (Allium cepa L): Onion is one of the major vegetable crops grown in the world.

The complex aroma, flavour, and lachrymatory characteristics of onion have been attributed to a variety of sulphur compounds. Allicin and its derivatives are one of the major sulphur-containing volatile compounds in Allium species such as onion, and Allicin is known to have curative as well as potential anti-carcinogenic, anti-mutagenic, and antimicrobial properties (Table 1) [18,19]. It is well known that both oil-soluble and water-soluble organo-sulphur compounds (OSC) are contained in onions, some of which have been shown to be chemo-preventive against carcinogenesis in animal models. Some studies have reported that dially sulphide (DAS) inhibits development of colon carcinomas, oesophageal carcinomas, pulmonary adenomas, and forestomach tumours in rodents when administered prior to carcinogen exposure [20]. However, Fukushima, Takada, Hori, and Wanibuchi [21] observed that water-soluble OSCs have inhibitory effect on rat liver carcinogenesis in second stage growth. S-Allylcysteine, S-propylcysteine, S-ethylcysteine, S-methylcysteine and cysteine, decreased GST-P-positive foci (Glutathione S-transferase placental form), particularly SMC and cysteine which caused significant reduction in the numbers and areas of GST-P-positive foci.

In addition, the World Health Organization supports the use of the onion bulb for the treatment of age-dependent changes in blood vessels and loss of appetite [22].

Furthermore, Mizuho and Shibamoto [23] showed that volatile samples of freeze-dried onions possess potent anti-inflammatory activity as well as a strong antioxidant property. The bioactive compounds in onion have been found to be capable of reducing enzymatic browning and/or oxidoreductase activity [24]. Several researches have shown that sulphydryl (SH or thiol) compounds are good inhibitors of polyphenol oxidase enzyme (PPO), major enzyme responsible for browning activity in fruits and vegetables [25,26]. Hence, onion extracts could be used as natural food ingredients for prevention of browning caused by PPO [27].

Fennel (Foeniculum vulgare): Fennel is a biennial medicinal and aromatic plant belonging to the family Apiaceae (Umbelliferae). It is a highly aromatic and flavourful herb with culinary and medicinal uses. Fennel seeds are anise like in aroma and are used as flavourings in baked goods, meat and fish dishes, ice cream, alcoholic beverages and herb mixtures [28]. Fennel seed extracts have been shown to have potential use in the treatment of glaucoma, as a diuretic and potential drug for hypertension treatment in animal studies. Extensive studies have been done on F. vulgare with the conclusion that the chemo preventive effect of fennel is generally attributed to its essential oil. Although, caution should be taken regarding some of the volatile components, in particular estragole (methylchavicol), which has been associated with the development of malignant tumours in rodents. Karlsen, Svendsen, Chingova, and Zolotovich [29] reported that the major constituents of sweet fennel (var. dulce) and bitter fennel (var. vulgare) include anethole, estragole, and fenchone, and additional 18 compounds extracted in the monoterpen fraction of the fruit vegetable. Alpha-pinene, camphene, beta-pinene, alpha-phellandrene, myrcene, limonene, beta-phellandrene, gamma-terpinene, cis-ocimene, terpinolene, and p-cymene were the minor volatile oil constituents of bitter fennel.

Both sweet and bitter varieties of fennel essential oils contain about 90% trans-anethole, 20% fenchone and small amount of limonene, camphor, alpha-pinene, and other additional minor volatile compounds [30]. The essential oils have been reported to possess anti-inflammatory, antioxidant and pro-oxidant activities [31]. Anethole has been reported to possess antimicrobial activity (Table 1) [32], and an active estrogenic agent, and a safe antithrombotic agent [33]. Rather et al. [34] reported that anethole increases milk secretion, promote menstruation, facilitates birth, and alleviates the symptoms of the male climacteric and increase libido. However, in some studies, it was shown that dienethole and photoanethole are the actual estrogenic agents.

Carrot (Daucus carota sativus): Daucus is a genus belonging to the Apiaceae family and consist of over 500 species widely spread around the world. For a long time, plants from this family have been used as spices or drugs. Carrot essential oils have been reported to have several bioactive properties such as antibacterial, fungicidal, hepatocellular regenerator, general tonic, and stimulant, lowering of high cholesterol, and cicatrization [40]. The oils of some subspecies of Daucus carota have been proven to possess antibacterial activity [41,42].

D. carota is the source of sesquiterpenic alcohols, carotol and daucol, and the sesquiterpene beta-caryophyllene. Carotol, one of the major sesquiterpene alcohols of Daucus carota seeds has a probable biogenesis from cis, trans-farnesol. Previous studies have shown that the chemical composition of Daucus species is more dominated by monoterpene hydrocarbons such as alpha-pinene and sabineene [43]. Jasicka-Misiak et al. [43], isolated the following terpenoids: carotol, beta-caryophyllene, daucol from the volatile components of carrot and tested their antifungal activity on strains of fungi belonging to the Alternaria family and a strain of Acremonium isolated from the surface of carrot seeds. The combination of these three terpenoids produced strong inhibitory effects on mycelium radial growth of Alternaria alternata. Although, it was observed that sesquiterpene beta-caryophyllene failed to have any effect. The activity of carotol was nearly as strong as the commercially available fungicide Funaben T (85%).

Various volatile compounds such as terpenes and varieties of aliphatic hydrocarbons (alcohol, aldehydes and ketones) isolated by hydro distillation of oils from Daucus species have been shown to have direct activity against many bacteria species. This antimicrobial action is attributed to the lipophilic character of their hydrocarbon skeleton and hydrophilic character of their functional group [44]. The ketone (undecan-2-one) has also been proven to possess both antimicrobial and nematocidal activities (Table 1) [45]. Glis’ic, Mišić, Stamenic, Zizovic, Asanin, and Skala [46] also discovered that carotol; the main volatile component isolated from essential oil of carrot fruit is most effective against gram-positive bacteria. Sabineene however exhibited a stronger antimicrobial effect against Bacillus subtilis, which have previously been proven to inhibit growth of Bacillus subtilis by Dorman, and Deans [47].
Flower part of vegetables

**Globe Artichoke (Cynara scolymus L.):** Many human diseases, including accelerated ageing, cancer, cardiovascular diseases, neurodegenerative diseases and inflammations, are generally linked to increase amount of free radicals [48]. Artichoke is an herbaceous plant native to the Mediterranean Basin. Globe artichoke is mostly used for food. However, various studies have demonstrated the health promoting properties of its extracts. Beta-selinene, one of the volatile constituents found in artichoke, has been reported to exhibit an antioxidant activity [49]. Eugenol and fenchone are also some of the volatile components of artichoke with biological activities (Table 1). Fenchone which is found in fennel leaves possess acaricidal activity against *D. farina* and *D. pteronyssinus* when used as direct contact application. On the other hand, eugenol has been reported to inhibit the reactive oxygen species (ROS) generation, intracellular calcium accumulation, and the subsequent mitochondrial membrane potential collapse [50]. In addition, eugenol inhibits cytochrome C release, and caspase-3 (CCLI) activation induced by oxidized low density lipoprotein (LDL). Another compound found in artichoke is xanthorrhizol, a natural sesquiterpenoid. Xanthorrhizol has been shown to possess protective effect against cisplatin-induced nephrotoxicity [27]. It also exhibits a potent neuroprotective effect on glutamate-induced neurotoxicity and reactive oxygen species (ROS) generation in the murine hippocampal HT22 cell line. H2O2-induced lipid peroxidation in rat brain homogenates was also found to be subdued by xanthorrhizol [51].

**Broccoli (Brassica oleracea L., *Italia* group):** Broccoli is classified in the *Italia* cultivar group of the species *Brassica oleracea*. It is a high source of vitamin C, and dietary fibre; it also contains multiple nutrients with potent anti-cancer properties, such as diindolylmethane and small amounts of selenium. Epidemiological observations suggested that high intake of fruit and vegetables could be associated with a reduced risk of cancer [3], and cruciferous vegetables, including broccoli, cabbage, cauliflower, and Brussels sprouts, seemed particularly beneficial in preventing carcinogenesis [52]. Researchers have shown that the volatile constituents responsible for these activities were the sulphur containing compounds, such as isothiocyanates (R-NCS) and their glucosinolates precursors [53], and indole-based constituents, such as indole-3-carbinol, 3,3′-di-indolylmethane, and indole-3-acetonitrile [54]. These volatile constituents were found to induce drug-metabolizing enzymes in cell culture and rodent tissue, and their chemopreventive activity was attributed to the increased detoxification of xenobiotic and carcinogens [55,56].

When broccoli cell structure is ruptured during processing, enzyme myrosinase comes into contact with glucoraphanin to form isothiocyanate sulforaphane (SF; 1-isothiocyanato-4-methylsulfinylbutane), and the related nitrile [57]. Sulforaphane has been considered to be the principal component responsible for the cancer prevention of broccoli [58]. Sulforaphane, an aliphatic isothiocyanate, has been isolated from broccoli as the major inducer of Phase II drug-metabolizing enzymes [59,60]. Isothiocyanate sulforaphane (ITCs) has been shown to inhibit tumor genesis which is induced by a wide variety of chemical carcinogens in animal models [61].

**Cauliflower (Brassica oleracea Botrytis):** Cauliflower like other Brassica family has the capacity to prevent cardiovascular diseases as well as to exert activity against some type of cancers [52]. Violet cauliflower extracts have shown significant antioxidant properties [62]. Pedras, Sarwar, Suchy, and Adio [63] isolated 3 different phytoalexins (secondary metabolites) from cauliflower which contain indolylisulfide and non-sulfur containing indolyl phytoalexin. The cauliflower A, an example of indolylisulfide exhibited the most antifungal activity against *S. sclerotiorum*. Isothiocyanate (ITCs) an enzymatic hydrolysis product of glucosinolates is particularly effective in inhibiting the germination of fungal pathogens: *B. cinerea, R. stolonifer, M. lazea, M. piriformis* and *P. expansum* [64]. Sisti, Amaglani, and Brandi [65] also showed that *B. oleracea* aqueous juice was able to inhibit *C. albicans* growth in a dose-dependent manner. Over 95% inhibition was recorded after 4 h of incubation with 15% juice. Cauliflower is also a good source of sulphur-containing volatiles and ITCs. Epidemiological studies have shown evidences over the years, that diet relatively high in cruciferous vegetable can reduce the risk incidence or progression of cancer.

The leaf part of vegetables

**Arugula (Eruca vesicaria subsp. Sativa):** Arugula also known as salad rocket is from the same Brassicaceae family as cabbage, broccoli and cauliflower. Several researches have been conducted to identify the main volatile constituents responsible for these protective effects of *Brassicaceae* vegetables [66]. One study identified 4-methylthiobutyl glucosinolate (glucoerucin), while another attributed the effects to the presence of 4-mercaptothyl glucosinolate (glucosatavin) [67]. The major volatile compounds in Arugula include sulphur/nitrogen containing compounds (4-methylthiobutyl isothiocyanate and 5-methylthiopentanenitrile), fatty acids, esters, and also volatile aldehydes [68]. Villatoro-Pulido, Font, Saha, Obregón-Cano, Anter, Muñoz-Serrano [69] also revealed that Arugula extracts and its sulforaphane were able to detoxify the genotoxic activity of hydrogen peroxide with inhibition rates ranging from 0.13-0.93. In addition, a possible association was established between the consumption of arugula and the antioxidant defence system of mammals.

Arugula has been reported to have the following properties: anti-oxidant, diuretic, astringent, anti-inflammatory for colitis, laxative, anti-phlogistic and an aid in digestion [70]. They have also been used as biological controls to inhibit pest development [71]. Lamy et al. [72] reported the chemopreventive potency of arugula extracts in HepG2 cells. They observed that Arugula exhibited anti-genotoxicity by reducing the benzo (a) pyrene-induced genotoxicity in a U-shaped manner, and that the compounds responsible for this chemopreventive activity were identified as isothiocyanate erucin, sulforaphane, erosilin and phenylethyl isothiocyanate. Literature survey reveals that Arugula leaves are anticorrosive, diuretic, stimulant and stomachic while the seed and seed powder have rubefacient and antibacterial properties respectively [73]. Rani et al. [74] also showed that both crude water extract and methanolic extract of Arugula exhibited varying degrees of microbial inhibition. Water extract showed moderate antifungal activity against *Spadicoides stoveri* and *Paecilomyces variotii*, while it showed significant antibacterial activity against *Hafnia alvei* and *Enterobacter agglomerans*.

**Water dropwort (Oenanthe javanica):** Water dropwort belongs to the family Umbelliferae and it is cultivated in marshy places of Asia and Australia. Water dropwort is known to have antimutagenic effect against aflatoxin B1 and a capacity to remove heavy metals, such as Cadmium [75]. The principal volatile compounds of water dropwort were α-copaene, carophyllene, α-cuprene, and a cembrene-type diterpene, incenseol [76]. Recent studies have shown that incenseol and its acetylated form incensole acetate, exhibits anti-inflammatory effect as well as several CNS-associated activities [77,78]. Similarly, tricyclic sesquiterpene, copaene has been shown to exhibit antioxidant and anti-carcinogenic features [79].
Stem part of vegetables

Celery (Apium graveolens): Celery belongs to the family Umbelliferae and it grows wild in Europe, the Mediterranean region and in Asia, west of the Himalayas. Seeds of the celery plant have been used for thousands of years in Ayurveda medicine. The volatile extracts of celery seeds are used in the perfume and pharmaceutical industries. All parts of this vegetable are known to be a remedy for one or more maladies. It has been reported to have insecticidal, bactericidal [80], and chemostatic effects [81]. The principal volatile constituents of celery are limonene, β-selinene, β-caryophyllene, sedanolde, cis-ocimene, apiole, 3-butylyphthalide, myrcene and 3-butyl-4,5-dihydrophthalade, [82,83]. Jawad, Suvarnalatha, Sankar, and Suresh [84] reported that sesquiterpene lactones from A. graveolens exhibited antimicrobial activity against Bacillus subtilis, Proteus vulgaris, and tested fungi, while Siapailene, Venskutonis, Sarkinas, and Cypiene [85] showed that root extracts which composed more of trans-ocimene, 3-methyl-4-ethylhexane and β-pinne [86] have high activity against B. cereus and Enterococcus faecalis. Celery has been used traditionally to treat many ailments such as rheumatism, rheumatoid arthritis, diuresis, and indigestion [87]. Alcoholic extracts of celery roots have been used to cure urinary disorders such as urinary stone, and used as kidney stimulant and cleanser. Furthermore, several studies have reported that celery seed has been useful for the treatment of urinary calculi, gut diseases, flatulence and gripping pains, reduction of visceral spasm and stimulation of the smooth muscle of the womb. Phthalide is not fully understood. A better knowledge of some variables of VOCs in common vegetable and their potential roles in the prevention of various diseases are reviewed. The volatile organic compounds with roles in health promoting activities in vegetables are Benzene propane nitrile, 1H-Indole-3-acetonitrile, Xanthorrhizol, Thymol, Carvarol, terpenoids, capsacian, and glucosinolates. Although several biological effects based on epidemiological studies can be scientifically explained, the mechanism of action of some effects of the above named compounds is not fully understood. A better knowledge of some variables of VOCs bioavailability, such as the kinetics of absorption, accumulation and elimination, will facilitate the design of such studies. The role of volatile organic compounds in health is still a fertile area of researches.

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