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Crucial facts about health benefits of popular cruciferous vegetables

Shivapriya Manchali[a], Kotamballi N. Chidambara Murthy[b,c,*], Bhimanagouda S. Patil[b]

[a]Department of Biotechnology and Crop Improvement, University of Horticultural Sciences, Bagalkot, GKVK Campus, Bengaluru 560 065, India

[b]Vegetable and Fruit Improvement Center, Department of Horticultural Sciences, Texas A&M University, College Station, TX 77845-2119, United States

[c]Triesta Sciences, HealthCare Global Oncology Hospital, P. Kalinga Rao Road, Sampangiramnagar, Bengaluru 560 027, India

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ABSTRACT

The lower incidences of many chronic diseases such as cancer and cardiovascular related ailments are associated with consumption of vegetables rich dietary regimes and this has been substantiated through numerous *in vitro*, pre-clinical and clinical investigations. Members of cruciferous family are cultivated and widely consumed universally as a part of daily diet. The major vegetables includes broccoli, cauliflower, radish, kale, brussels sprouts, watercress and cabbage that are used either fresh (salads), steamed or cooked. Besides nutritional components, these vegetables are also rich in health beneficial secondary metabolites, which include sulfur containing glucosinolates and S-methylcysteine sulfoxide, flavonoids, anthocyanins, coumarins, carotenoids, antioxidant enzymes, terpenes and other minor compounds. Based on the worldwide popularity and health benefits of these vegetables, this review provides collective information on nutritional and health benefits. In addition, information on evidence based therapeutic and prophylactic benefits of commonly used cruciferous vegetables are discussed with emphasis on cancer and cardiovascular disease. Some of the unique mechanisms of cancer inhibition such as effect on Nrf2, polymorphism, anti-inflammatory, inhibition of histone deacetylase activity and influence on estrogen metabolism are also included.

1. Brief history

Brassica oleracea and *Brassica rapa* of Brassicaceae (Cruciferae) family comprise many important vegetables that are grown and consumed worldwide. The vast genetic diversity existing in this family might have encouraged the primitive man to domesticate, cultivate, select and propagate morphologically distinct and desirable crops from the wild types. The cultivars are described based on the morphology of edible plant part and geographical identification (Dixon, 2007). In *B. oleracea* L. ($2n = 18$), which is of European origin, the human selection has resulted in a wide array of vegetable groups. Different plant parts such as, leaf, inflorescence, stem were the targets for modification (Ordás & Cartea, 2008). The wild cabbage resembling leafy canola plant was grown as a leafy vegetable in the Mediterranean region. Selective propagation of plants with enlarged leaves led to the development of kale in 5th century BC. The botanical name of kale is *B. oleracea* and variety *acephala* which means 'cabbage of the vegetable garden without a head'. The preference for a larger compact structure of leaf gradually transformed the wild species to cabbage with a terminal head that has a cluster of tender leaves. This

* *Corresponding author at:* Triesta Sciences, #8, HealthCare Global Oncology Hospital, P. Kalinga Rao Road, Sampangiramnagar, Bengaluru 560 027, India. Tel.: +91 80 4020 6105; fax: +91 80 4020 6106.
E-mail address: kncmurthy@gmail.com (K.N. Chidambara Murthy).
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process took very long time and was completed in the 1st century AD. Eventually, cabbage was introduced to different parts of the world by Europeans (Dixon, 2007). The varietal name *capitata* for cabbage is due to its head. White headed, red headed and savoy are the types available in cabbage. Selection of kale plants with short fleshy stems gave birth to swollen or flattened edible stemmed kohlrabi (*B. oleracea* var. *gongylodes*) in Central and Southern Europe (Hanelt, 1997).

Cauliflower and broccoli are believed to have evolved in the Eastern coast of the Mediterranean region. During the Roman period, germplasm exchange took place due to trade between many Mediterranean countries and the adaptation of these cruciferous crops to different places resulted in distinct forms of cauliflower and broccoli (Branca, 2008). Edible immature flower bud was the target for selection. Cauliflower plant with large tender flowering heads was developed in the 15th century and a hundred years later, Broccoli was born in Italy with a varietal name *italica*. Since the cauliflower head resembles a grape bunch, it is also called as *botrytis*.

It is believed that Brussels sprouts developed around the city of Brussels, Belgium in 18th century (Dixon, 2007) and later became an important vegetable in North Eastern Europe. The varietal name '*gemmifera*' means 'garden cabbage bearing gems'. Chinese kale (*B. oleracea* var. *alboglabra*), also known as 'Chinese broccoli' is widely used in China and it might have moved to China from the Mediterranean region.

Chinese cabbage (*B. rapa* var. *pekinensis*) is one of the most important vegetables in the *B. rapa* (campestris) ($2n = 20$) group and is a native of China. It is believed to have originated by the natural crossing of 'Pak choi' and 'turnip'. Based on the head type, Chinese cabbage is available in different forms. Turnip (*B. rapa*) is the oldest *B. rapa* crop and its origin is unknown (Dixon, 2007). Radish (*Raphanus sativus*) is native of China and is mentioned in historical records of the Egyptian, Roman and Greek civilizations. Rutabaga, collard greens and Chinese mustard are other important cruciferous vegetables cultivated.

2. Bioactive molecules

2.1. *Nutritive*

Major nutritional components of cruciferous vegetables are, protein, carbohydrate and vitamins (ascorbic acid, folic acid, tocopherols and provitamin-A). Iron, calcium, selenium, copper, manganese and zinc are the essential mineral elements in these vegetables (Singh, Kawatra, & Sehgal, 2001). The protein content of cruciferous vegetables ranges from 1.0% to 3.3% (w/w) on fresh weight basis. Highest amount of protein is reported in kale (3.3%), while radish contains less than 1% protein on fresh weight basis. Collard green is known for relatively highest fiber content with 4.6% (w/w fresh weight basis), followed by broccoli (30.4% w/w dry weight) and cauliflower (26.7% w/w dry weight basis). Negligible amount of fat (less than 1.0%) in cruciferous vegetables makes them an important constituent of a low fat and heart friendly diet. Watercress has relatively highest amount of fat (~1%), while most of the other cruciferous vegetables are free from dietary fat. Cruciferous vegetables also serve as a good source of carbohydrates, which ranges from 0.3% to 10% (w/w fresh weight basis). Major nutritional compositions of commonly consumed cruciferous vegetables are listed in Table 1. Cruciferous vegetables are also a good source of vitamin C, the content in broccoli is more than 50 mg/100 g of fresh weight. One of the accession of broccoli, NS-50 is known to contain up to 82 mg vitamin C/100 g on fresh weight basis (Singh, Upadhyay, Prasad, Bahadur, & Rai, 2007). Maximum mean β-carotene content of major cruciferous vegetables is 0.5–1.0 mg/100 g of fresh weight (Mangels, Holden, Beecher, Forman, & Lanza, 1993). Cruciferous vegetables also contain

Table 1 – Major nutritional components of commonly used cruciferous vegetables.

Cruciferous vegetable	Protein	Fiber	Fat	Carbohydrate
	g/100 g fresh weight			
Arugula	2.58	1.60	0.66	3.65
Bok choy	1.42	1.42	0	2.85
Broccoli	2.82	30.40[a]	0.37	6.64
Brussels sprouts	2.55	26.94[a]	0.51	8.67
Cabbage	1.53 (green) 0.97 (red)	23.24[a]	0	6.00
Cauliflower	29.9[a]	26.70[a]	0.45[b]	4.11[b]
Chinese cabbage	1.50	1.00	0.20	2.20
Collard greens	3.00	4.60	0.40	7.10
Daikon	<2.00	<2.00	0	4.00
Kale	3.28	1.94	0.74	10.0
Kohlrabi	1.70	3.62	0.07	6.22
Radish	0.68	37.40[a]	0.08	3.45
Turnips	0.90	1.76	0.10	6.43
Watercress	3.00	1.50	1.00	0.35

Note: Values are converted from content per serving or fresh average vegetable weight. Additional source – http://www.nutritiondata.com/facts. Refs. (Anderson & Bridges, 1988; Khanum, Siddalinga Swamy, Sudarshana Krishna, Santhanam, & Viswanathan, 2000).
[a] Dry weight basis.
[b] Boiled.

Table 2 – Macro and micronutrients composition of commonly consumed cruciferous vegetables.

Cruciferous vegetable	Macronutrients (mg/g of fresh weight)					Micronutrients (μg/g of fresh weight)				
	Phosphorous	Potassium	Magnesium	Sodium	Calcium	Iron	Selenium	Copper	Manganese	Zinc
Arugula	0.50	3.70	0.45	0.25	1.60	0	0	0	0	0
Bok choy	0.37	2.50	0.19	0.92	1.06	8.00	–	–	1.42	1.00
Broccoli	0.66	3.17	0.21	0.33	0.47	7.70	0.025	–	2.20	4.40
Brussels sprouts	0.69	3.89	0.23	0.25	0.42	14.00	0.016	1.10	3.40	4.50
Cabbage (domestic)	0.23	2.46	0.15	0.18	0.47	5.60	0.009	0.22	1.50	1.70
Cauliflower[a]	0.44	3.03	0.15	0.30	0.22	4.00	0.006	–	2.00	0.30
Chinese cabbage	0.37	2.51	0.19	0.65	1.05	8.50	0.004	–	1.40	1.40
Radish	0.23	2.27	0.16	0.21	0.27	4.10	0.007	1.20	0.30	1.50
Kale	0.56	4.46	0.34	0.43	1.35	16.00	0.009	3.00	7.50	0.45
Kohlrabi	0.46	3.34	0.19	0.20	0.24	3.70	0.007	1.50	1.50	0
Turnips (green)	0.42	2.96	0.31	0.40	1.90	10.00	0.013	3.60	5.40	1.80
Watercress	0.60	3.30	0.20	0.40	1.20	3.00	0.009	0	3.00	0

Note: '–' not reported; '0' not detected. Values are converted from content per serving or fresh average vegetable weight.
[a] Contain 0.001 μg/g fluoride (source of information – http://www.nutritiondata.com/facts).

α-tocopherol, and the maximum mean content of 0.47 mg/100 g has been reported in broccoli (Granado et al., 2006). Total phenolic content of cruciferous vegetables ranges from 9.92 to 82.90 mg/100 g of fresh weight, and the highest content of phenolics was found in broccoli (Zhang & Hamauzu, 2004). Calcium, phosphorous, magnesium, sodium and potassium constitute major macro elements and iron, selenium, copper, manganese and zinc are micronutrients found in cruciferous vegetables. Approximate composition of these micro and macronutrients in some of the commonly consumed cruciferous vegetables is listed in Table 2.

2.2. *Secondary metabolites (non-nutritive)*

In cruciferous vegetables, nitrogen containing compounds constitute a major class of secondary metabolites, whereas glucosinolates (GSL) and S-methylcystine sulfoxide (SMCSO) are the major sulfur compounds. Flavonoids, anthocyanins and carotenoids constitute biologically active colored compounds. Apart from these, polyphenols, coumarins, therapeutic antioxidant enzymes, and terpenes constitutes major health beneficial compounds. Chemical structures of most abundant and representative compounds from each class of cruciferous vegetables from major class are represented in Fig. 1.

2.2.1. *Sulfur containing compounds*

Among the phytochemicals in cruciferous vegetables, GSLs and SMCSO are the major constituents. More than 120 GSLs and the precursors of isothiocyanates have been identified in plants (Hirai et al., 2007). These compounds are known for their fungicidal, bactericidal, nematocidal and allelopathic properties (Moreno, Carvajal, Lopez-Berenguer, & Garcia-Viguera, 2006) and are recently gaining popularity as cancer chemopreventive and chemotherapeutic agents. GSL of plants are classified as sulfur containing, branched aliphatic, aromatic aryl and aromatic indoles. The enzyme '*myrosinase*', which is released along with GSL upon injury, is known to convert GSL into isothiocyanates. In addition to this, human gut flora will also convert GSL to isothiocyanates, which are available in serum for biological activity (Shahidi, Gabon, Rubin, & Naczk, 1990). Hence, the biological activities related to cruciferous vegetables are focused on isothiocyanates. Cooking, steaming and other heat involved processes are known to inactivate the activity of *myrosinase* enzyme leading to lower conversion of GSL into isothiocyanates. Some more sulfur compounds have been identified in the soil after degradation of cruciferous plat tissues, this includes, 2-propenyl glucosinolate, volatile compounds such as carbon disulfide, dimethyldisulfide, dimethylsulfide and methanethiol (Bending & Lincoln, 1999).

The major classes of GSLs, found in cruciferous plants are broadly classified as aliphatic, ω-methylthioalkyl, aromatic and heterocyclic glucosinolates. The GSLs are biosynthesized in cruciferous plants in major three steps of naturally occurring chemical reactions namely, side chain elongation, glucone biosynthesis and side chain modification. *N*-hydroxylation of a precursor amino acid is the first step in which side chain of amino acid will be elongated. This is followed by decarboxylation of elongated amino acid derivative to form an aldoxime (glucone). Following this step, sulfur group will be introduced to form thiohydroxamic acid. Addition of UDP-glucose to thiohydroxamic acid lead to the formation of desulfoglucosinolate. Addition of second sulfur group by 3′-phospho adenosine-5′-phosphosulfate (PAPS) leads to the formation of glucosinolate (Fahey, Zalcmann, & Talalay, 2001).

Rapid reactive nature of isothiocyanates due to presence of highly electrophilic central carbon atom is responsible for their interaction with phase-I and II enzymes to detoxify carcinogens. Metabolism of carcinogens and acceleration of their excretion are the major mechanism by which the sulfur compounds can prevent cancer. Activation of both phase-I and II enzymes, carcinogen-DNA adduct formation and modification of accompanying nucleotides are the major events observed during cancer prevention mechanism studies of

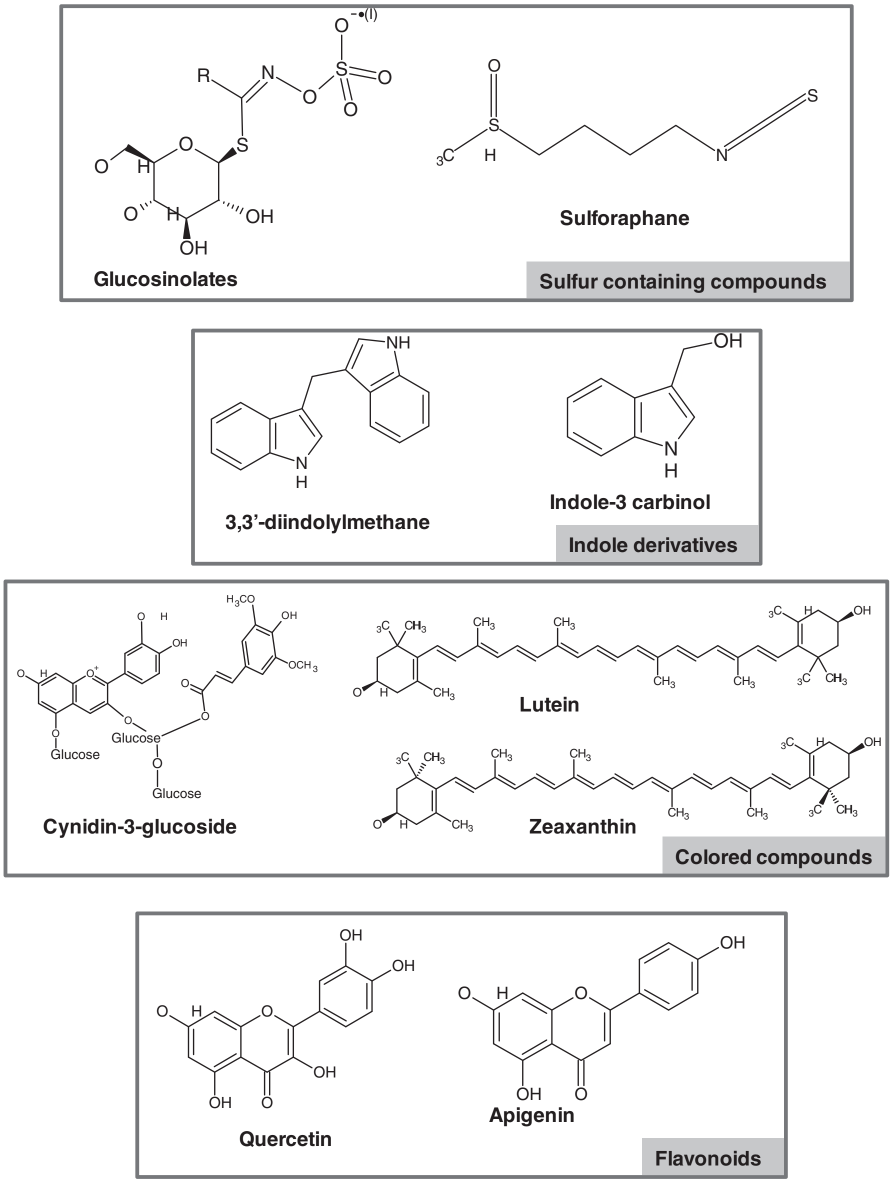

Fig. 1 – Chemical structure of biologically significant compounds of cruciferous vegetables.

isothiocyanates and the same is discussed further in detail (Zhang & Talalay, 1994).

2.2.2. *Phenolic compounds*

Tannins, phenolic acids, anthocyanidins, flavonols, coumarins and flavones are commonly found phenolics of cruciferous vegetables. The tannin content of broccoli, cauliflower and white cabbage are 0.41, 0.56 and 0.50 mg/g of dry weight, respectively. The phenolic acid content of broccoli is highest among the cruciferous vegetables, which accounts for 8.69 mg/g of dry weight (Heimler, Vignolini, Dini, Vincieri, & Romani, 2006). Dietary flavonoids composition is represented mainly based on the content of three flavonols namely, quercetin, myricetin, and kaempferol and two flavones apigenin and luteolin (Aherne & O'Brien, 2002). Average content of quercetin in red broccoli is 1.0–5.0 mg/100 g of edible portion and that of kaempferol is 1.0–2.5 mg/100 g of edible portion. Brussels sprouts contain 0.95 and 0.30 mg/100 g of kaempferol and quercetin, respectively. Red cabbage contains only quercetin where as green cabbage contains both kaempferol and quercetin. Raw Chinese kale contains upto 26.74 mg/100 g of kaempferol and 7.71 mg/100 g of quercetin (Chun, Chung, & Song, 2007; Harnly et al., 2006). Red cabbage contains upto 322 mg/100 g and red radish contains upto 116 mg/100 g of anthocyanins in the fresh consumable portion (Wu et al., 2006). Mean β-carotene content of 18 cabbage cultivars is reported to be 0.05 mg/100 g of fresh weight and 0.08 and 0.14 mg/100 g in two major cultivars of cauliflower and brussels sprouts, respectively. Mean β-carotene content of five commercial broccoli cultivars is 0.81 mg/100 g of fresh weight (Singh et al., 2007).

2.2.3. *Other bioactive compounds*

Phytosterols and other terpenoids constitutes other important bioactive compounds. Cruciferous vegetables are also a good source of phytosterols, which are known for their cancer preventive and cardioprotective activity. Brassicasterol is another sterol found in broccoli and other cruciferous vegetables. The content of sterols differs in part of plants propagated and cultivars. Florets contained relatively higher amount of sterols compared to stems and a maximum of 230 mg/100 g d.w. sterol has been reported (Gajewski, PrzybyŁ, Kosakowska, & Szymczak, 2009). Storage of vegetables under controlled atmosphere (5% CO_2 + 2% O_2 and 93% air) is known to prevent degradation of sterol compared to normal conditions (0% CO_2 + 21% O_2 and 79% air). Therefore, to get maximum health benefits of sterols and other phytochemicals in cruciferous vegetables, use of controlled atmosphere is recommended (Gajewski, PrzybyŁ, Bajer, & JarienĖ, 2011).

3. Health benefits

3.1. *Cruciferous vegetables and cancer*

Most of the research on cruciferous vegetables prior to 1970 was focused on prevention of crop diseases and development of different cultivars. Some of the clinical and pre-clinical investigations using cruciferous vegetables in different cancers were reported in mid and late 1970s (Loub, Wattenberg, & Davis, 1975; Merrlin & Graham, 1979; Wattenberg & Loub, 1978). Cohort and case control studies conducted between 1980 and 1990 suggested an inverse relation between the consumption of cruciferous vegetables and incidences of colorectal, pancreatic, lung, breast, gastrointestinal and ovarian cancer (Benito et al., 1990; Chyou, Nomura, Hankin, & Stemmermann, 1990; Graham et al., 1982; Le Marchand, Yoshizawa, Kolonel, Hankin, & Goodman, 1989; Olsen, Mandel, Gibson, Wattenberg, & Schuman, 1989; Shu, Gao, Yuan, Ziegler, & Brinton, 1989; Wargovich, 1988). Among many research findings published during 1990–2000 on the health benefits of cruciferous vegetables, research from the Johns Hopkins University is a milestone in the area of cancer chemoprevention. The research published by Prof. Talalay and his group in 1997 demonstrated a higher induction of cancer protective enzymes by bioactive molecules of broccoli sprouts (Fahey, Zhang, & Talalay, 1997). It was observed that 3 days old sprouts of broccoli and cauliflower contained 10–100 times higher amount of glucoraphanin compared to that in the corresponding matured plants. These glucoraphanin rich sprouts were highly effective in reducing the incidence and development of mammary tumors in 7,12-dimethylbenz(*a*)anthracene (DMBA) treated rats. The report concluded that small quantities of cruciferous sprouts may offer more protection against risk of cancer as compared to large quantities of mature vegetables. Another commentary published in the same journal explains the clinical efficacy of cruciferous vegetables as inducers of carcinogen-detoxifying enzymes (Nestle, 1997). One of the recent studies from Dr. Fahey's laboratory reports that daily consumption of broccoli sprouts for 2 months (human subjects were asked to consume 70 g/day of glucoraphanin rich 3 day old germinated broccoli sprouts) can reduce *Helicobacter pylori* induced oxidative stress and helps in chemoprevention of gastritis in experimental animals and humans (Yanaka et al., 2009). For details on biosynthesis and distribution of glucosinolates and isothiocyanates in plants, readers are referred to a review (Fahey et al., 2001). Research by Dr. Talalay and group in The Johns Hopkins University made a huge impact on the utilization of cruciferous vegetables, especially sprouts, in US and rest of the world. Research since 2000 is focused more on understanding the cancer preventive and anti-inflammatory mechanism of bioactive molecules in cruciferous vegetables (Cheung, Khor, & Kong, 2009; Keck & Finley, 2004). Cruciferous bioactive molecules have a unique mode of inhibiting inflammation through NFκB. Sulforaphane has shown inhibition of lipopolysaccharide (LPS) induced pro-inflammatory and pro-carcinogenic factors like, NO, prostaglandin E_2 and TNF-α. It is also known for selective reduction in DNA binding of NFκB, without interfering with the translocation of NFκB. Additionally, sulforaphane is also known for suppression of LPS induced Cox-2 and inducible nitric oxide synthase (Heiss, Herhaus, Klimo, Bartsch, & Gerhäuser, 2001). Based on the existing information, Table 3 summarizes cancer chemopreventive ability of selected bioactive molecules and their mechanisms of action.

3.1.1. *Antioxidant activity and induction of oxidative stress*

Antioxidant activity of cruciferous vegetables is due to both bioactive compounds and enzymes such as catalase, superoxide dismutase (SOD) and peroxidase, which are found in fresh vegetables. The content of SOD ranges from 4.8 to 7.6 (min/g)$^{-1}$ FW (fresh weight) in some of the varieties cultivated in India. The peroxidase content in these vegetables varies from 415.0 to −5314.0 μmol tetraguaiacol/min/g FW and content of catalase ranges from 14.2 to −258.8 mM H_2O_2 reduced/min/g fresh weight (Singh, Sharma, & Singh, 2010).

Induction of oxidative stress in cancer cell is one of the cytotoxicity mechanisms by which bioactive molecules derived from cruciferous vegetable can kill cancer cells. Generation of oxidative stress through induction of cytochrome P450 leading to DNA damage by glucoraphanin (the bioprecursor of sulforaphane) was observed in experimental animals (Paolini et al., 2004).

3.1.2. *Induction phase I and II enzymes*

Bioactive molecules from cruciferous vegetables are known to induce phase II enzymes, which help in metabolism of xenobiotics to prevent potent carcinogenesis. These enzymes also help in acceleration and disposal of xenobiotic metabolites and inhibition of phase-I enzymes, which otherwise known to activate carcinogens. Sulforaphane and its derivatives have demonstrated significant induction of glutathione-S transferase (GST) and quinone reductase (QR) activity in chemically challenged animals (Zhang, Talalay, Cho, & Posner, 1992). Both 7-methylsulfinylheptyl and 8-methylsulfinyloctyl isothiocyanates present in watercress have shown induction of QR in murine hepatoma Hepa 1c1c7 cells (Rose, Faulkner, Williamson, & Mithen, 2000). A synthetic analog of sulforaphane, (±)-4-methylsulfinyl-1-(S-methyldithiocarbamyl)-butane has shown induction of NAD(P)H and QR in cultured murine Hepa 1c1c7 cell and its two mutants (Gerhauser et al., 1997). Inhibition of phase-I enzymes along with induction of phase-II enzymes by isothiocyanates is attributed to the ability of broccoli to reduce breast cancer risk (Ambrosone et al., 2004). Chemoprevention of breast cancer through induction

Table 3 – Cancer inhibition mechanisms by selected bioactive molecules of cruciferous vegetables.

Bioactive compound/s	Cell line/model used	Major mechanism of inhibition	Reference
Sulforaphane	HT-29 cells	Cell cycle arrest and apoptosis	Gamet-Payrastre et al. (2000)
	Carcinogen challenged animals	Inhibition of phase I enzymes and/or induction of phase II enzymes	Hecht (1999)
	MDA-MB-231, MDA-MB-468, MCF-7 and T47D human breast cancer cells	Caspase(s) mediated cell specific apoptosis	Pledgie-Tracy, Sobolewski, and Davidson (2007)
	PC-3 cells	Caspase(s) mediated apoptosis	Singh et al. (2004)
	DU-145 prostate cancer cells	Cell cycle arrest	Wang et al. (2004)
	PC-3 prostate cancer cells	Combating ROS and induction of apoptosis	Singh et al. (2005)
	PC-3 and LNCaP human prostate cancer cells	Induction of autophagy	Herman-Antosiewicz, Johnson, and Singh (2006)
	MIA PaCa-2 and PANC-1 pancreatic cancer cells	Apoptosis, cell cycle arrest, and oxidative stress pathways	Pham et al. (2004)
	DU145 cells	c-Jun N-terminal kinase mediated G2/M phase of cell cycle arrest	Cho et al. (2005)
	PC-3 and LNCaP cells	Inhibitor of apoptosis family proteins and Apaf-1	Choi et al. (2007)
D,L-Sulforaphane	A549 human non small lung cancer cells	Induction of apoptosis	Mi et al. (2007)
Phenethyl isothiocyanate and sulforaphane	Azoxymethane induced F344 rats	Suppression of colonic aberrant crypt foci (ACF)	Chung, Conaway, Rao, and Reddy (2000)
	JB6 P mouse epidermal cell line	p53 mediated apoptosis	Huang, Ma, Li, Hecht, and Dong (1998)
Indole 3-carbinol	MCF-7 and MDAMB-231 cells	Induction of estradiol metabolism and the related cytochrome P-450 system	Tiwari, Guo, Bradlow, Telang, and Osborne (1994)
	MCF-7 cells	Expression of cyclin-dependent kinase-6 and induction of G_1 cell cycle arrest	Cover et al. (1998)
	PC-3 cells	G1 phase arrest and apoptosis	Chinni, Li, Upadhyay, Koppolu, and Sarkar (2001)
Indole-3-carbinol and 3,3′-diindolylmethane	PC-3, LNCaP and DU-145 cells	p53 dependant apoptosis	Nachshon-Kedmi, Yannai, Haj, and Fares (2003)

of phase-II enzymes by indole-3 carbinol is reported in DMBA induced animals (Grubbs et al., 2008). Synergistic induction of GST and QR by two of the breakdown products of Glucosinolate, namely indole-3-carbinol and crambene is also reported in experimental animals suggesting the activity of glucosinolates metabolites. Oral treatment of both indole-3-carbinol and crambene for 7 days has demonstrated a significant induction of GST, QR and ethoxyresorufin O-deethylase (EROD), which is an indicator of P450-dependant mono-oxygenases activity (Nho & Jeffery, 2001). Induction of glutathione S-transferase (GST)-π by sulforaphane was also observed in different human prostate cancer cells (Brooks, Paton, & Vidanes, 2001). Fig. 2 depicts the pharmacokinetic and pharmacodynamics behavior of isothiocyanates derived from cruciferous vegetable.

Another major pathway followed for detoxication by bioactive molecules of cruciferous vegetables is Nrf2 dependant pathway. Nrf2 is considered as master transcription factor for regulation of antioxidants and its association with cancer is well documented by number of studies (Talalay & Fahey, 2001). Under normal conditions, Nrf2 is sequestered in cytoplasm by KEAP (Kelch-like ECH associating protein) 1. Under oxidative stress or influence of some phytomolecules, Nrf2 dissociates from KEAP1 and is translocated to the nucleus, where it binds to ARE (antioxidant response element) and transactivates phase II detoxifying and antioxidant enzymes. There are number of studies explaining the activation of Nrf2 pathway by bioactive molecules of cruciferous vegetables to help detoxication of chemically induced carcinogens (Lampe & Peterson, 2002; Xu et al., 2006).

3.1.3. *Tumor inhibition and apoptosis*

Numerous research reports explain the ability of cruciferous bioactive compounds to inhibit tumors in experimental animals. Among the bioactive compounds of cruciferous vegetables explored for cancer inhibition, isothiocyanates, indole-3-carbinol (Murillo & Mehta, 2001) and phytoalexins (Mehta et al., 1995) are highly promising. Sulforaphane has demonstrated induction of apoptosis and cell cycle arrest in human colon adenocarcinoma (HT-29) cells (Gamet-Payrastre

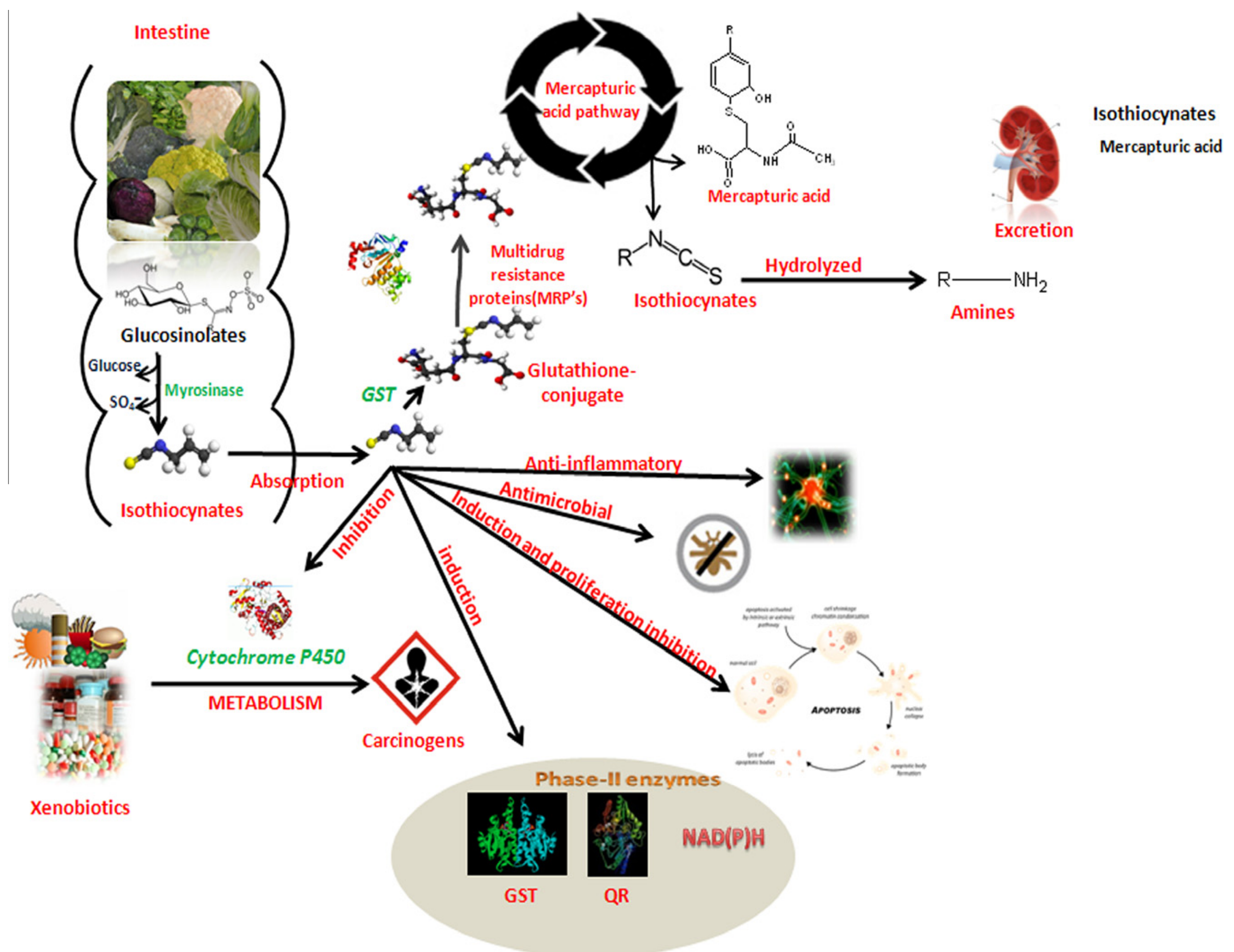

Fig. 2 – Pharmacokinetic and major mechanism of cancer prevention by isothiocyanates: a major bioactive compound of cruciferous vegetables.

et al., 2000). Induction of caspase mediated apoptosis in androgen independent prostate cancer cell is reported (Singh, Xiao, Lew, Dhir, & Singh, 2004). Isothiocyanates are known to inhibit both androgen dependant (LNCaP) and independent (PC-3) prostate cancer cells through arrest of cells in G2/M phase and induction of apoptosis (Xiao et al., 2003). The major targets of isothiocyanates in inhibiting cancer cells include induction of caspase dependant and independent apoptosis, activation of c-Jun N-terminal Kinase and cell cycle arrest (Chen, Wang, Kong, & Tan, 1998; Yu, Mandlekar, Harvey, Ucker, & Kong, 1998). Isothiocyanates also modulate signaling kinase pathways (MAPK, PI3K, PKC and PERK) and cell signal mediators like, AP-1 and NFκB (Jakubikova, Bao, & Sedlak, 2005; Keum, Jeong, & Tony Kong, 2004).

3.1.4. *Inhibitors of histone deacetylase activity*

Acetylation of histone is known to affect gene expression and is associated with the development of cancer. Compounds capable of inhibiting the enzyme activity are known to arrest cell growth, induce cell death or apoptosis and inhibit tumor through alteration in gene transcription levels (Marks et al., 2001). Both isothiocyanates and sulforaphane are known to inhibit the histone deacetylase activity in number of cancer cells and animal models (Dashwood & Ho, 2007; Myzak, Dashwood, Orner, Ho, & Dashwood, 2006; Myzak, Hardin, Wang, Dashwood, & Ho, 2006). Molecules which can inhibit histone deacetylase activity are of great importance in chemoprevention of cancer. Other dietary derived compounds known for the activity are butyrate and diallyl disulfide (DADS) found in garlic (Myzak et al., 2006).

3.1.5. *Role in estrogen metabolism and induction of polymorphism*

Indole and diindolylmethane are the major bioactive molecules of cruciferous plants known to act on enzymes responsible for estrogen metabolism. Among the dietary indoles, 3,3′-diindolylmethane (DIM) is the most potent inducer of estrogen 2-hydroxylase activity (Jellinck et al., 1993). The net estrone level is reduced due to estrogen blocking activity of 2-hydroxylated products, which is associated with lower risk of breast cancer. The increased ratio of 2-OH:16-OH is associated with breast, uterine and cervical dysplasia (Zeligs, 1998). The cancer preventive potency of DIM may be due its ability to maintain the higher levels of 2-hydroxyestrone level and the

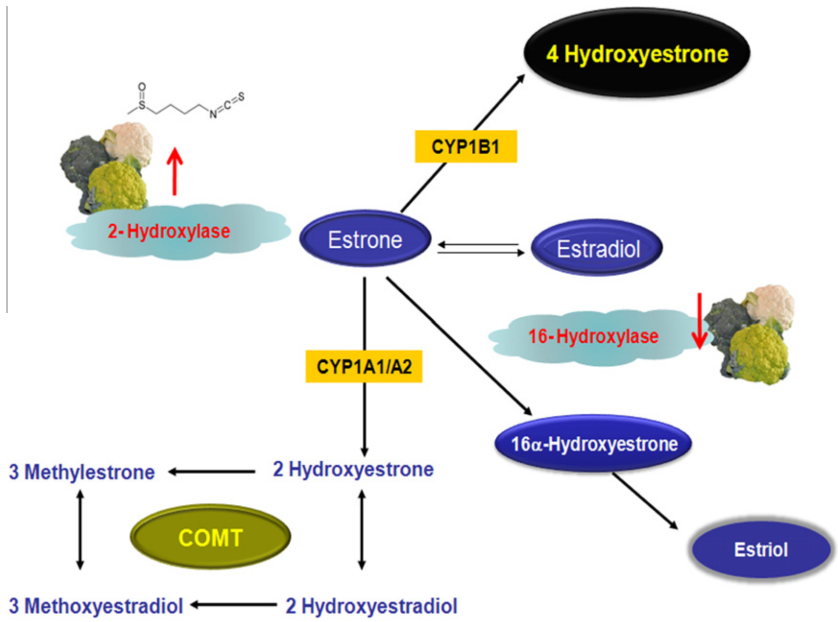

Fig. 3 – Interference of bioactive molecules of Broccoli and other cruciferous vegetables in estrogen metabolism [adopted from (Zeligs, 1998)].

same is currently under clinical investigation. Fig. 3 depicts the role of broccoli in human estrogen metabolism.

Metabolites of glucosinolates are known to modulate biotransformation enzyme systems, such as cytochrome P450 and conjugating enzymes. Human intervention studies have suggested that continuous consumption of cruciferous vegetables can affect CYP1A family, phase-II enzymes (GST and UGT) and alter steroid hormone metabolism. For detailed information on role of cruciferous vegetables on biotransformation and prevention of cancer through alteration in polymorphism, refer to an article by Lampe and Peterson (2002).

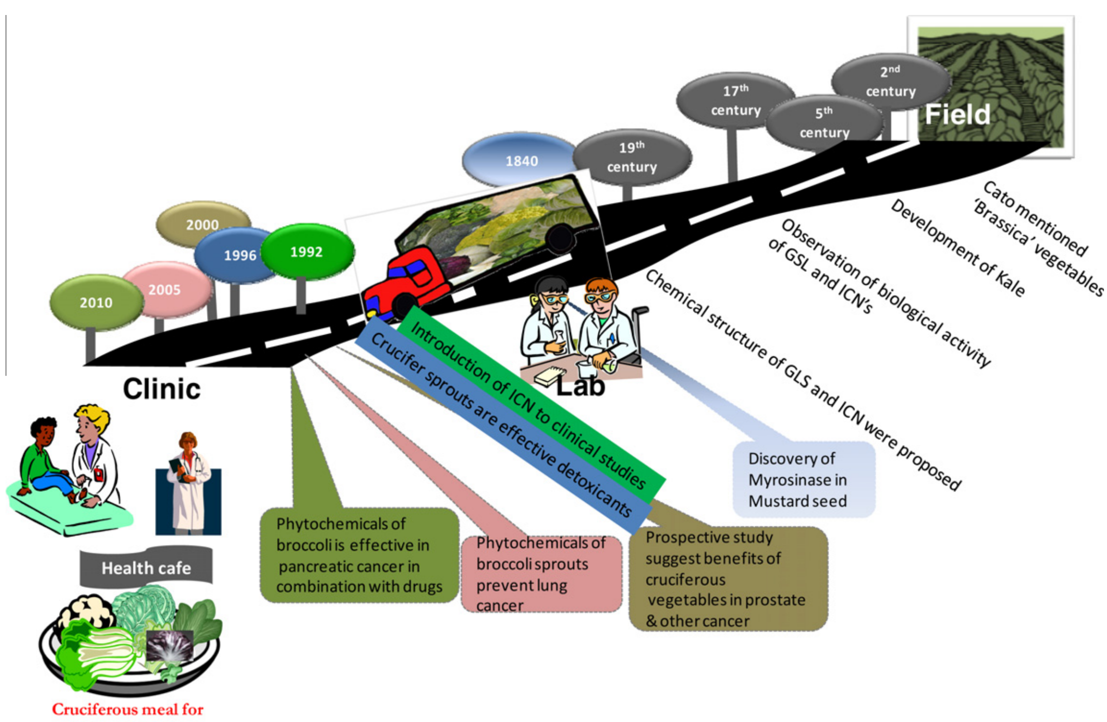

Fig. 4 – Cartoon depicting the journey of cruciferous vegetable research from field to clinic via laboratory. This represent only selected event related to origin and health benefits based on the relevant findings that are discussed in the paper (GSL – glucosinolates; ICN – isothiocyanates).

Fig. 5 – Most popular cruciferous vegetables sold in local vegetable market. Images of cauliflower (white and colored), cabbage (green and red), broccoli, daikon, brussels sprouts, Chinese cabbage, bok choy and watercress were captured by senior author from local vegetable market (Farm patch, Bryan, Texas) and collage was made using Adobe Photoshop software version CS4. (For interpretation of the references in color in this figure legend, the reader is referred to the web version of this article.)

3.1.6. *Epidemiological evidences*

Consumption of vegetables rich in isothiocyanates resulted in protection against lung cancer in Chinese women. Weekly intake of more than 53.0 μM isothiocyanates has resulted in significant reduction of lung cancer as measured by *GSTM1* and *GSTT1* polymorphisms in 420 smoking and non-smoking subjects (Zhao et al., 2001). A similar study was performed using 63,257 middle-aged subjects of colorectal cancer in which incidence of cancer between high and low isothiocyanates consuming individuals consist of both GSTM1 and T1 null genotypes) was compared. There was 57% reduction of colorectal cancer in individuals with high isothiocyanates consumption (Seow et al., 2002). Result from one of the population-based study suggests an inverse relation between consumption of cruciferous vegetables with incidences of lung cancer in multiethnic population (Le Marchand et al., 1989). Iowa women's health study indicates higher consumption of broccoli resulted in an odds ratio of 0.72, suggesting the benefit of bioactive molecules in prevention of lung cancer (Steinmetz, Potter, & Folsom, 1993). One of the prospective studies involving 29,361 subjects (of which 1338 were prostate cancer positive) suggests that only cruciferous vegetables are capable of preventing prostate cancer and its symptoms but not other fruits and vegetables. Among the cruciferous vegetables, broccoli and cauliflower were found to be more effective with relative risk of 0.55 and 0.48 between >1 servings/week and <1 serving/month, respectively (Kirsh et al., 2007). Comparison of multiple studies on consumption of cruciferous vegetables suggests that highest cruciferous vegetables consuming individuals had 22% lower incidences of lung cancer as observed in case–control study and 17% lower in cohort studies compared to those with lowest intake. Individuals with *GSTM1* and *GSTT1* double null genotypes demonstrated strongest inverse association (Lam et al., 2009).

3.2. *Cruciferous vegetables and heart health*

Bioactive compounds of cruciferous vegetables help in heart health mainly through their ability to reduce LDL, combat free radicals and up-regulate GST activity (reduction of oxidative stress) as revealed by *in vitro*, *in vivo* and clinical studies.

3.2.1. *In vitro* studies

One of the most abundant bioactive molecules of cruciferous vegetables, sulforaphane, is capable of up-regulating GST in impaired aortic smooth muscle cells (SMCs) in spontaneously hypertensive rats (SHR). This up-regulated GST activity was correlated with reduction in oxidative stress, which is the major culprit in cardiovascular complications (Wu & Juurlink, 2001). Sulforaphane is known to protect the heart through initiation of survival signals and activation of redox signaling of thioredoxin enzymes, which are known to facilitate other proteins by cysteine thiol-disulfide exchange (Angeloni et al., 2009).

3.2.2. *In vivo* studies

Feeding of rats with a diet rich in green and yellow vegetables (broccoli is one of the ingredient) for 16 weeks has resulted in significant reduction of atherosclerotic markers, such as cholesteryl ester content, plasma total serum cholesterol, VLDL + ILDL cholesterol and serum amyloid-A (Adams, Golden, Chen, Register, & Gugger, 2006). Results from *in vivo* study suggests that sulforaphane protects ischemic injury of heart through induction of Nrf2-dependent phase-II enzymes like, Mn-superoxide dismutase (SOD), catalase and hemeoxygenase-1 in experimental animals (Piao et al., 2010). Induction of ischemia for 30 min in rats fed with broccoli extract (1.5 g/kg b.w. containing approximately 23.6 ± 1.5 μg/g of sulforaphane and 0.065 ± 2.8 μg/g of selenium) for 30 days demonstrated protection of rats from ischemia. Feeding rats with broccoli resulted in improvement of post-ischemic ventricular function, reduction in the myocardial infarcts size and prevention of caspase-3 and cytochrome-*c* mediated apoptosis of cardiomyocytes. The study concludes that the consumption of broccoli results in cardioprotection by activating survival signals through redox cycling of thioredoxins (Mukherjee, Gangopadhyay, & Das, 2007). One of the recent study has demonstrated that feeding of freeze dried broccoli sprouts can help in cholesterol homeostasis in dietary hypercholesterolemia induced Syrian hamsters (Rodríguez-Cantú et al., 2011).

3.2.3. *Clinical studies*

Association of fruit and vegetable consumption with decreased incidences of coronary heart disease is also demonstrated through clinical studies. This was supported by 14 years of follow-up with Nurse's health study and 8 years follow-up of Health Professionals study (Joshipura et al., 1999). A clinical study of 12 subjects demonstrated that, the consumption of broccoli sprouts for only 1 week reduced markers of oxidative stress along with increased metabolism of cholesterol (Murashima, Watanabe, Zhuo, Uehara, & Kurashige, 2004). Result of women's health study, which consisted of more than 39,000 professional women with no history of cardiovascular disease, suggested the relative risk (RR) of 0.45 between extreme quintiles consumption groups. Since, cruciferous vegetables are among the vegetables considered in the study, results clearly indicate the positive influence of cruciferous vegetables in prevention of cardiovascular disease (Liu et al., 2000). Because of its benefits, cauliflower juice is also used as supplement in nutrition for cardiovascular health (Hsia & Fan, 2003).

Thus, apart from cancer chemoprevention, cruciferous vegetables are also known to support cardiac health. Other than sulforaphane, benefits in cardiac health may also be due to selenium (Virtamo et al., 1985) and other bioactive molecules like, flavonoids (Hertog, Feskens, Kromhout, Hollman, & Katan, 1993), anthocyanins (Mazza, 2007), polyphenols (Duthie, Duthie, & Kyle, 2000) and antioxidant enzymes (Blomhoff, 2005).

3.3. Other health benefits

Direct and indirect research evidences demonstrates the benefits of cruciferous vegetables in prevention of metabolic disorders, asthma and Alzheimer's disease, along with antimicrobial activity against number of pathogens. Among the metabolic syndromes, the role of isothiocyanates in diabetics is well demonstrated. A number of prospective studies suggest that the consumption of vegetable rich diet (broccoli and other cruciferous vegetables constitute significant portion) is associated with a reduced incidence of type-II diabetes (Liu et al., 2004; van Dam, Rimm, Willett, Stampfer, & Hu, 2002; Villegas et al., 2008). A 12 year follow-up study indicates that a higher intake of vegetables is also associated with a reduced incidence of obesity. The study included broccoli, cabbage, cauliflower, and brussels sprouts and subjects were middle aged women (He et al., 2004). Long term treatment with 200 mg indole 3-carbinol twice a day has been demonstrated to be effective in chemoprevention of respiratory papillomatosis (RRP), a upper respiratory abstraction caused by human papilloma virus (Rosen & Bryson, 2004). Prevention of pollution induced oxidative stress by GST through Nrf2 signaling pathway is reported from sulforaphane, indirectly suggesting the benefits in prevention of inflammation associated respiratory disorders (Riedl, 2008; Wan & Diaz-Sanchez, 2006). Since, Alzheimer's disease is associated with oxidative stress (Butterfield, Drake, Pocernich, & Castegna, 2001) and bioactive molecules of cruciferous vegetables are also known to prevent oxidative stress, these may be the benefits of consuming cruciferous vegetables to prevent Alzheimer's disease. Further, a clinical investigation suggests that a higher intake of vegetables is also associated with slower rate of cognitive decline in older age (Morris, Evans, Tangney, Bienias, & Wilson, 2006). Water, methanol and crude protein extracts of cruciferous vegetables (includes cauliflower, broccoli, cabbage, Chinese radish, Chinese kale, and Chinese kitam) have shown antimicrobial effect against pathogenic microbial stain. The activity was found to be significant against Gram-negative bacteria such as, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Salmonella* serovar typhimurium, *Escherichia coli* and *Shigella sonnei* compared to Gram-positive organisms (Hu et al., 2004).

4. Conclusion

In summary, cruciferous vegetables contain a myriad of biologically active molecules and nutritional components and are a unique source of biologically active sulfur and nitrogen containing compounds. Research suggests that consumption of cruciferous vegetables is associated with several health benefits. Activation of phase-II enzymes and induction of apoptosis are the key mechanism by which cruciferous vegetables results in health benefits. Biotechnological and agricultural approaches to produce cruciferous vegetables with optimum content of bioactive molecules that are responsible for health benefits may be of great utility. Popularity of cruciferous vegetables is also evidenced through their cultivation and consumption worldwide. A cartoon demonstrating the major discoveries in cruciferous vegetables based on some of the information in the paper is depicted in Fig. 4. The Fig. 5 is a portrait made from most popular cruciferous vegetables sold in one of the vegetable market in the Unites States.

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