

CANCER PREVENTING PROPERTIES OF CRUCIFEROUS VEGETABLES

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Summary

Health-promoting phytonutrients in cruciferous vegetables have been gaining attention for their powerful effects in combating cancer. This review concerns anticancer properties of cruciferous green vegetables of “Brassica” genus such as broccoli, kale, Brussels sprouts, watercress. The role and mechanisms of action of cruciferous active compounds such as sulforaphane, indole-3-carbinol, diindolylmethane and phenethyl isothiocyanate in protection against cancer and cancer-fighting are discussed. Losses of nutrients and active compounds during cooking, microwaving, and blanching of vegetables which may be more substantial than commonly perceived are also reviewed.

key words: cruciferous vegetables, cancer, glucosinolates, isothiocyanates, sulforaphane, indole-3-carbinol, diindolylmethane

INTRODUCTION

According to report published in 2007 by the World Cancer Research Fund, UK (Expert Report) a startling 30-40% of cancers are directly linked to improper diet and related factors. Human population as well as animal studies consistently show that diet high in cruciferous vegetables, cabbage, cauliflower and especially leafy green vegetables of the “Brassica” genus such as broccoli, Brussels sprouts, collard and watercress are associated with a lower incidence of certain cancers including lung, colon, breast, ovarian and bladder cancers (Higdon *et al.* 2007, Fowke 2007, Juge *et al.* 2007, Zhao *et al.* 2007). The remarkable compounds derived from cruciferous vegetables appear to work through various mechanisms to inhibit cancer cells. One group of bioactive compounds is known as glucosinolates. Glucosinolates are converted to isothiocyanates such as sulforaphane and indoles such as indole-3-carbinol (I3C). These compounds inhibit cancer by various mechanisms within the body. The conversion of glucosinolates to isothiocyanates occurs naturally in several ways. One pathway is through the presence of myrosinase, an enzyme found in the cells of cruciferous vegetables, however the process of cooking of vegeta-

bles destroys much of the naturally available myrosinase. Glucosinolates obtained from cooked cruciferous vegetables can still be converted to isothiocyanates inside the body but much less efficiently than when myrosinase is available. The conversion can occur in the colon where native gut bacteria hydrolyze the glucosinolates (Getahun & Hung 1999, Johnson 2002).

Protective effects of sulforaphane against cancer

Sulforaphane activates gene expression, helping to clear carcinogenic substances from the body more quickly. It triggers the liver to produce detoxification enzymes called Phase II enzymes, which help neutralize cancer-causing substances (Hwang & Jeffery 2005, Wang *et al.* 2004, Cornblatt *et al.* 2007). Such beneficial enzymes induced by cruciferous vegetables include quinone reductase and glutathione-S-transferase. In experimental studies of cancer formation, quinone reductase has been shown to dose dependently inhibit the growth of cancer cells. In a study of patients with lung cancer a high intake of cruciferous vegetables has been found to reduce the risk of lung cancer by 39% only in those with a beneficial variant of the gene called GSTM1. This gene produces the enzyme glutathione-S-transferase, which detoxifies carcinogens in tobacco smoke (Wang *et al.* 2004). Other studies reveal that sulforaphane helps support a healthy immune system which is a key component in staving off cancer. Sulforaphane has been found to significantly enhance the production of several chemicals that are involved in the immune response such as interleukin-2 and interferon-gamma (Thejass & Kuttan 2006). In other research sulforaphane has been shown to have a more direct effect on cancer prevention especially in colon cancer, inducing cancer cells to destroy themselves. This was seen in the study in which animals were genetically bred to develop intestinal polyps, a conditions that leads to tumour formation. This group of animals was then fed sulforaphane and found to have higher rates of apoptosis (cell suicide) and smaller tumours that grew more slowly than animals who received no sulforaphane (Khor *et al.* 2006).

The role of cruciferous vegetables compounds indole-3-carbinol (I3C) and diindolylmethane (DIM) in cancer risk reduction

Numerous cell culture, animal and human studies have demonstrated that indole-3-carbinol suppress cancer growth and induces programmed cell death in a variety of tumours, including those associated with breast, prostate, leukaemia and colon cancers (Aggarwal & Ichikawa 2005). Some authors consider I3C to be especially valuable in protecting against hormone-dependent cancers such as certain breast, cervical and prostate cancers due to its ability to favourably influence the human body's balance of estrogens (Aggarwal & Ichikawa 2005, Ashok *et al.* 2001, 2002, Yuan *et al.* 1999). For example I3C inhibits cancer cell growth by interfering with the production of proteins involved in abnormal cellular reproduction and by promoting the production of tumour suppressor proteins (Aggarwal & Ichikawa 2005, Firestone & Bjeldanes 2003, Sarkar *et al.* 2003). I3C regulates many genes that are important for the control of cell cycle,

cell proliferation, signal transduction and other cellular processes and also induces apoptosis (programmed cell death) in cancer cells by interfering with the production of compounds that cancer ordinarily produces to resist apoptosis (Sarkar & Li 2004, Nachshon-Kedmi *et al.* 2003). In liver and intestinal lining I3C is believed to enhance the functioning of critical enzyme systems that are responsible for detoxifying the body of harmful potentially cancer-causing chemicals. Such toxic substances may be ingested in food or drink or be absorbed through environmental contact. These enzyme systems, technically known as Phase I and Phase II enzymes, alter the chemical structure of toxic compounds in order to detoxify them (Leibelt *et al.* 2003, Crowell *et al.* 2006). Some researchers suggest that I3C may also prevent cancer by interfering with angiogenesis, a process critical to the body's defence against cancer (Wu *et al.* 2005). Angiogenesis is the process of formation of new blood vessels that tumours require for their survival and metastasis (spread of cancer). I3C also induces breast cancer cells to become more responsive to interferon gamma, an important immune system chemical associated with protecting the body from disease (Chatterji *et al.* 2004).

Beneficial effects of I3C are partly assisted by its condensation product 3,3'-diindolylmethane (DIM). It interrupts the ability of cancer cells to reproduce and affects the expression of a large number of genes that are related to the control of carcinogenesis, cell survival and physiologic behaviour (Pledge-Tracy *et al.* 2007, Pappa *et al.* 2007, Li *et al.* 2005). DIM reduces biochemical markers of angiogenesis and strongly inhibits the development of human breast tumour in an animal model which provides evidence for the anti-angiogenic properties of this dietary indole (Chang *et al.* 2005).

The most important mechanism of action of I3C and DIM is modulating estrogen metabolism. This is because estrogen receptors are present on the surface of virtually every type of tissue in the bodies of the men and women and are associated with several hormone-dependent cancers. The body modifies or metabolizes estrogens through two mutually exclusive pathways, which lead to compounds with different biological activities. Estradiol is the primary estrogen in circulation and one of the most active. It is metabolized to a number of other chemicals, all with some degree of estrogenic activity. The enzymes 2-hydroxylase and 16- α -hydroxylase help metabolize estrogens. One pathway results in estradiol's conversion to a less potent form of estrogen 2-hydroxyestron (2-OHE1) while the other pathway increases production of more toxic estrogen metabolite 16- α -hydroxyestrone (16 α -OHE1). The theory that certain estrogen metabolites can contribute to cancer was confirmed by the data gathered from over 10,000 Italian women over more than five years to determine how dietary and hormonal factors influence breast cancer risk. It was found that women were much less likely to develop breast cancer, when they had higher levels of the less potent estrogen metabolite 2-OHE1 (Muti *et al.* 2000). The higher ratio of "good" 2-OHE1 to "bad" 16 α -OHE1 is significantly associated with a reduced risk of breast cancer. Subsequent studies of different populations have confirmed this finding. The ratio of these two estrogen me-

tabolites is now widely regarded as an indicator for the risk of breast and other hormone associated cancers with a higher 2-OHE1 : 16 α -OHE1 ratio considered desirable (Auborn *et al.* 2003, Fowke *et al.* 2003, Meng *et al.* 2000). The 2-OHE1 : 16 α -OHE1 ratio was examined for prostate cancer risk. Although the study results failed to achieve statistical significance, elevated 2-OHE1 levels in urine suggest a reduced risk of prostate cancer while elevated 16 α -OHE1 levels are associated with an increased risk. Men with the highest values of 16 α -OHE1 are twice as likely to have prostate cancer as men with the highest levels of 2-OHE1 (Muti *et al.* 2002). The cruciferous vegetable compounds, I3C and DIM, are effective in shifting the metabolism of estradiol to a more beneficial pathway thus reducing levels of toxic 16 α -OHE1 and increasing levels of protective 2-OHE1. This beneficial modulation of estrogen metabolism correlated with reduced risk of breast and other cancers including cervical and prostate (Fowke *et al.* 2003, Kristal & Lampe 2002, Fowke *et al.* 2000, Muti *et al.* 2000).

Potent cancer protection from watercress and broccoli

Cruciferous vegetables such as watercress and broccoli are rich sources of anticancer compounds known as phenethyl isothiocyanate (PEITC) (Rose *et al.* 2000, Palaniswamy *et al.* 2003). Extracts of watercress and broccoli suppress an enzyme, metalloproteinase-9, closely associated with the invasive potential of breast cancer (Rose *et al.* 2005a). Furthermore, in laboratory models of cellular activity watercress isothiocyanates suppress production of pro-inflammatory compounds such as nitric oxide (NO) and prostaglandins (PG), which are associated with numerous pathological conditions including chronic inflammation and cancer. This effect may contribute to the anticancer activity of cruciferous vegetables (Rose *et al.* 2005b). Epidemiological evidence shows a strong association between greater intake of cruciferous vegetables and reduced risk of prostate cancer. It was found that conjugate of PEITC which is abundant in watercress inhibits proliferation and tumourigenesis of prostate cancer cells growing in culture (Chiao *et al.* 2004). Phenethyl isothiocyanate may reduce cancer risk in smokers by blocking the cytochrome P450-mediated metabolic activation of the common nitrosamine to its potent carcinogenic forms (Conaway *et al.* 1996, Ribnicky *et al.* 2001). It appears that even after isothiocyanates are modified for efficient removal from the body in urine, they remain active against cancer. Urine containing conjugated isothiocyanates which are stored in the bladder while awaiting removal, act on the tissue lining the bladder to prevent carcinoma. This is precisely the site where most bladder tumours arise, so that isothiocyanates such as those in watercress may be useful for the prevention of bladder cancer (Tang & Zhang 2004). PEITC and other dietary isothiocyanates from cruciferous vegetables tend to be cleared from the body through urinary excretion. They are able to limit cancer cell proliferation of human leukaemia after only three hours of exposure (Zhang *et al.* 2003). The compounds in watercress induce both Phase I and Phase II liver enzymes, an effect that may explain its ability to inhibit chemically-induced DNA damage

from a wide variety of compounds. DNA damage can lead to carcinogenesis (Lhoste *et al.* 2004).

Role of phytochemicals from cruciferous vegetables in neutralizing environmental toxins

Carcinogenic estrogen-like compounds in the environment called xenoestrogens are ingested by people from plastics used in beverage bottles and food containers, industrial chemicals and pesticides. They can trigger onset or progression of cancer. By mimicking estrogens, xenoestrogens influence hormonally-regulated processes and induce changes in growth factors, which can set the stage for cancer (Starek 2003). Particularly carcinogenic xenoestrogens are the environmental contaminants-polychlorinated biphenyls (PCBs). Dangerously high levels of PCBs have been found in adults and children living in areas where these chemicals have contaminated the soil water and air. Some researchers believe PCBs are responsible for increases the incidence of allergies, autoimmune diseases, and hormone-dependent cancers (Inadera 2006, DeCastro *et al.* 2006). PCBs have made their way into the food chain particularly in certain types of sea food such as salmon (Burreau *et al.* 2006, Johnson-Restrepo *et al.* 2005). Numerous studies demonstrate that PCBs have a multitude of adverse effects on human health. Urban dwelling men who eat fish not only have the high levels of PCBs and related toxins but also have a greater incidence of male infertility indicators (Hauser *et al.* 2003). Exposure to PCBs may adversely affect the brain alerting mood and concentration and has been linked to increased rates of endometriosis in women, a chronic condition associated with pelvic pain and infertility (Peper *et al.* 2005, Louis *et al.* 2005). Although it is almost impossible to completely avoid these contaminants it was shown that it is possible to protect people against them by consuming optimal amounts of healthful phytochemicals from cruciferous vegetables to provide additional DNA protection from reactive oxygen species (Rogan 2006, Fowke *et al.* 2006). These phytochemicals, which include I3C and other compounds, enhance the effectiveness of the liver primary detoxification system enzymes Phase I and Phase II, which help transform harmful toxins and carcinogens into harmless compounds and reduce systemic oxidative stress independent of the vitamins and mineral content of these vegetables (Bradfield & Bjeldanes 1991, Nho & Jeffery 2001, Larsen-Su & Williams 1996, Crowell *et al.* 2006, Lhoste *et al.* 2004).

Gastrointestinal digestion of glucosinolates and synergistic action of broccoli bioactive compounds

Very little is known about the fate of broccoli bioactive compounds such as glucosinolates during the digestion process and particularly their fate in the food matrix under the gastric and intestinal conditions and the effect of these conditions on the stability of these compounds. In the work of Vallejo *et al.* (2004) broccoli was submitted to digestion under *in vitro* gastrointestinal conditions (pH, temperature, enzyme and chemical conditions). The technique

which they used differentiated among the compounds associated with macromolecules in soluble and insoluble form and those that are freely soluble. It allows the evaluation of the chemical stability of the broccoli compounds under simulated physiological conditions. This study showed gastric digestion of broccoli causes high losses (69%) in glucosinolates. On the contrary the remaining glucosinolates were only slightly affected by intestinal digestion conditions (12% additional loss). It is remarkable that in broccoli the availability of total glucosinolates under *in vitro* gastrointestinal conditions is almost three fold higher than the availability of total flavonoids and close to four fold higher than availability of hydroxycinnamoyl derivatives whereas the availability of vitamin C is similar to glucosinolates. Aliphatic glucosinolates are much more stable than indolic derivatives; only 27% is lost on the gastric digestion compared with indolic, which suffers losses of 73% (Vallejo *et al.* 2004). High loss of glucosinolates during gastric digestion could be explained by the high degradation of these compounds to nitriles at gastric pH (~3) and their low stability at intestinal pH (~7), leading to a decomposition into their secondary reaction products - isothiocyanates (Fenwick *et al.* 1983).

Interactions among different compounds in complex mixture can be positive or negative. Positive interactions that intensify the potency of bioactive product are generally called potentiation (Lila & Raskin 2005). Investigations of food matrix influences on bioactivity show that broccoli diets containing pre-hydrolyzed glucosinolates are significantly more potent than diets using comparable levels of purified sulforaphane (Keck *et al.* 2003). Sulforaphane delivered in the broccoli matrix may be less susceptible to binding by proteins, thus this phytochemical is detected in higher concentrations in the urine post-feeding. In rats fed broccoli with intact glucosinolates, quinone reductase up-regulation (a biomarker for anti-carcinogenesis) is significantly higher in both liver and colon than in animals on a control diet or on diets containing sulforaphane produced *in situ* by hydrolysis. Purified sulforaphane is less active than unfractionated broccoli components presented in a matrix, which suggests that other components in this vegetable (quercetin, other glucosinolate hydrolysis products or S-methylcysteine sulfoxide) potentiate bioactivity. Similarly glucosinolate derivatives from other cruciferous vegetables were evaluated in terms of influence on Phase II detoxification enzymes glutathione-S-transferase, quinone reductase, and glutathione reductase. The mixture of derivatives provides more potent up-regulation (increase response to a stimulus) of the enzymes than single components and two of the breakdown products, in particular cranbene and I3C, demonstrate synergy responsible for the majority of the enzyme up-regulation (Staack *et al.* 1998, Nho & Jeffery 2001).

Variation of glucosinolates content in broccoli florets

A significant variation in the level of glucosinolates in broccoli result from cultivar, variation in environmental and agronomic factors such as water availability (irrigation), soil composition (mineral and organic nutrients) as well as from intensity of sulphur fertilization (Kushad *et al.* 1999, Vallejo *et al.* 2002,

Vallejo *et al.* 2003, Borkowski *et al.* 2008). It was shown that glucoraphanin content varies depending on season of year and agricultural conditions in which broccoli grown. According to Kushad *et al.* (1999) the content of glucoraphanin in 50 cultivated forms of broccoli is very variable and ranges from 0.8 to 21.7 $\mu\text{mol}\cdot\text{g}^{-1}$ dry weight.

High individual variation among glucosinolates occurs in Volta F₁ broccoli plants that are cultivated in identical agricultural and climatic conditions (Borkowski *et al.* 2008). The results of this research are summarized in Table 1.

Table 1. Average content of glucosinolates of 15 florets of broccoli cv. Volta F₁ (source: Borkowski *et al.* 2008)

Glucosinolate	Content ($\mu\text{mol}\cdot\text{g}^{-1}$ dry weight)	Coefficient of variability (%)
Glucoiberin	2.84	12.61
Progoitrin	0.16	34.22
Glucoraphanin	17.95	14.84
Gluconapolipherin	0.37	13.74
Glucoalysin	0.11	18.11
Gluconapin	Traces	-
Glucoiberivin	Traces	-
Glucoerucin	Traces	-
Gluconasturin	0.11	18.11
4-Hydroxybrassicin	0.77	27.32
Glucobrassicin	7.17	13.51
4-Metoxylucobrassicin	1.55	7.61
Neoglucobrassicin	4.12	24.44
Total glucosinolates	34.5	14.24

Losses of nutrients and bioactive compounds after cooking of broccoli

Leafy green cruciferous vegetables of “Brassica” genus such as broccoli, kale, Brussels sprouts, watercress are a rich source of vitamins and minerals. Watercress provides a plentiful amount of lutein and zeaxanthin carotenoids that are essential for eyes and cardiovascular health as well as a considerable amount of vitamins A, C and K (Table 3). Lopez-Berenguer *et al.* (2007) investigating the effects of various methods of cooking of broccoli showed that steaming causes the least loss of nutrients. Microwaving broccoli results in a loss of 97%, 74% and 87% of the major antioxidant compounds, flavonoids, sinapics and caffeoyl-quinic derivatives, respectively. In comparison, steaming broccoli results in a loss of only 11%, 0% and 8% respectively, of the same antioxidants. Most of the bioactive compounds are water soluble and during heating they leach in a high percentage into the cooking water. It is recommended cooking vegetables in the minimum amount of water (as in steaming) in order to minimize losses of nutrients (Table 2). Blanching of vegetables prior to freezing causes losses of 20-30% of antioxidant activity and one third of vitamin C content. Only slight further losses occur during frozen storage. Most bioactive compounds remain stable (Puupponen-Pimiä *et al.* 2003).

Table 2. Chosen nutrient values (per 100 grams of edible portion) of broccoli (*Brassica oleracea* L. var. *italica*) (source: USDA National Database for Standard Reference, 2008)

Nutrient	Units	Broccoli raw	Broccoli cooked, boiled, drained without salt
Proximates			
Water	g	89.3	89.3
Energy	kcal	34	35
Protein	g	2.82	2.38
Total lipid (fat)	g	0.37	0.41
Ash	g	0.87	0.77
Carbohydrates by difference	g	6.64	7.18
Sugars total	g	1.70	1.39
Sucrose	g	0.10	0.08
Glucose	g	0.49	0.49
Fructose	g	0.68	0.74
Lactose	g	0.21	0.00
Fiber total dietary	g	2.6	3.3
Minerals			
Calcium Ca	mg	47	40
Iron Fe	mg	0.73	0.67
Magnesium Mg	mg	21	21
Potassium K	mg	316	293
Manganese Mn	mg	0.21	0.194
Selenium Se	µg	2.5	1.6
Vitamins and active compounds			
Vitamin C (total ascorbic acid)	mg	89.2	64.9
Thiamin	mg	0.071	0.063
Riboflavin	mg	0.117	0.123
Niacin	mg	0.639	0.553
Panthothenic acid	mg	0.573	0.616
Vitamin B-6	mg	0.175	0.200
Folate total	mg	0.063	0.108
Vitamin A	IU	623	1548
Vitamin E (α-tokopherol)	mg	0.78	1.45
β-carotene	mg	0.361	0.929
α-carotene	mg	0.025	0.000
Vitamin K (phylloquinone)	mg	0.102	0.141
Lutein + zeaxanthin	mg	1.403	1.08

Table 3. Chosen nutrient values of watercress (*Nasturtium officinale*) (source: USDA National Database for Standard Reference, 2008)

Nutrient	Units	Value per 100 grams of edible portion of watercress raw
Proximates		
Water	g	95.11
Energy	Kcal	11
Protein	g	2.30
Total lipid (fat)	g	0.10
Ash	g	1.20
Carbohydrates by difference	g	1.29
Sugars total	g	0.20
Fiber total dietary	g	0.50
Minerals		
Calcium Ca	mg	120
Iron Fe	mg	0.20
Magnesium Mg	mg	21
Potassium K	mg	330
Manganese Mn	mg	0.244
Selenium Se	µg	0.9
Vitamins and active compounds		
Vitamin C (total ascorbic acid)	mg	43
Thiamin	mg	0.090
Riboflavin	mg	0.120
Niacin	mg	0.200
Pantothenic acid	mg	0.310
Vitamin B-6	mg	0.129
Folate total	mg	0.009
Vitamin A	IU	3191
Vitamin E (α -tocopherol)	mg	1.00
β -carotene	mg	1.914
α -carotene	mg	0.000
Vitamin K (phylloquinone)	mg	0.250
Lutein + zeaxanthin	mg	5.767

Boiling for a typical time period causes a loss of 56% of the folate in broccoli while steaming causes no significant loss (McKillop *et al.* 2002). Broccoli florets lightly stir-fried in extra virgin olive oil or sunflower oil retain similar glucosinolate and vitamin C levels as uncooked ones (Moreno *et al.* 2007).

Natural phytonutrients derived from cruciferous vegetables such as broccoli, kale, Brussels sprouts and watercress offer powerful, broad spectrum support for maintaining healthy estrogen metabolism and protecting against the ubiquitous, cancer-provoking agents encountered every day in our environment. Incorporating these extraordinarily potent, plant-based compounds in a daily supplementation program is a safe, effective and inexpensive way to guard against many of today's most common and lethal cancers.

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PRZECIW NOWOTWOROWE WŁAŚCIWOŚCI WARZYW Z RODZINY KRZYŻOWYCH (*Cruciferae*)

Streszczenie

Warzywa z rodziny krzyżowych, a szczególnie zielone z rodzaju *Brassica*, jak brokuł, jarmuż, kapusta brukselska, rzeżucha, posiadają znaczące właściwości przeciw nowotworowe. Przedyskutowano rolę oraz mechanizmy działania takich aktywnych związków warzyw krzyżowych jak sulforafan, indol-3-karbinol, diindolylmetan oraz izotiocyanian fenetylu w zwalczaniu raka. Opisano również straty składników odżywczych i aktywnych związków w czasie blanszowania, gotowania warzyw w wodzie, parze i mikrofalach.