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Pharmacognocy review

Inhibition of endocrine function by botanical agents

II. *Cruciferae*

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Vegetable products with anticarcinogenic properties

CURRENTLY, INTEREST IN CRUCIFEROUS PLANTS centers on the vegetables of the *Brassica* genus that have shown cancer-protecting capability. Epidemiologic studies have shown a dose-response reduction in risk of cancer of the colon, rectum and bladder.*(1)* The presence of a glucosinolate (GS) (previously known as mustard oil-glucoside or thioglucoside) containing an indolylmethyl group which is commonly called glucobrassicin is generally credited for this effect. With mechanical rupture of *Brassica* plant tissue, enzymatic breakdown of GS produces a number of significant compounds *(Figure 1)*. From glucobrassicin these include indole-3-acetonitrile (IAN) and indole-3-carbinol (I3C) which rapidly converts to 3,3'-diindolylmethane (I33') and other indoles.*(2)* The particular indoles formed depend somewhat on the pH with IAN forming at pH 3-4 and I3C predominant at pH 7. Thiocyanate (SCN) ion is a byproduct of I3C formation. Increased activity by the anticarcinogenic aryl hydrocarbon hydroxylase enzyme system in the liver and small intestines of rats was induced by Brussels sprouts, cabbage and cauliflower due to these indoles, especially I3C.*(3)* I3C and I33' given orally prior to carcinogen administration inhibited mammary tumor formation, and all 3 indoles inhibited neoplasia of the forestomach in mice.*(4)* Excretion of I3C and its metabolites, especially I33', is via the urine and bile.*(5)* Successive increases in I3C doses given prior produced dose-related decreases in the binding of the administered carcinogen aflatoxin B1 to hepatic DNA in vivo in trout.*(6)* While tumor promotion from I3C given after aflatoxin B1 administration also occurred in trout, the inhibitory activity is more likely to supersede promotion under human exposure conditions.*(7)* The GS products occur in cooked as well as raw *Brassica* vegetables.*(2,8)*

Another CRUCIFERAE GS product, the oxazolidinethione (OZT) R-goitrin, also reduces aflatoxin B1-DNA binding and increases aflatoxin B1-thiol excretion by acting as a potent inducer of hepatic glutathione S-transferase.*(9)* The IAN prevalent in *Brassica* vegetables,*(8)* like I3C, also increases the activity of the glutathione S-transferase system that detoxifies chemical carcinogens. Still another type of cruciferous GS product, the isothiocyanate (ITC) benzyl-ITC, does the same.*(10)* ITC also inhibits induced mam-

ABBREVIATIONS: SCN=thiocyanate, ITC=isothiocyanate, A=allyl, B=benzyl, HB=p--hydroxybenzyl, MS= methylsulfonylpropyl, MSB= 4-methylsulfonylbutyl, MSP=3-methylsulfonopropyl, MTB=4-methylthio-3-butenyl, P= pentenyl, PE= phenylethyl, OZT= oxazolidinethione, D=5-dimethyl, E=ethyl, M=4-methyl, Ph= 5-phenyl, V= (-)5-vinyl, +V= (+)5-vinyl, BC= benzylcyanide, CEB= 1-cyano-3,4-epthiobutane, CEP= 1-cyano-2,3-epithiopropane, CHB= 1-cyano-2-hydroxy-3-butene, CHE=1-cyano-2-hydroxy-3,4-epithiobutane, IAN= indole-3-acetonitrile, MCT=4-methyl-1-cyanothiobutane, PPN=3-phenyl-proprionitrile.

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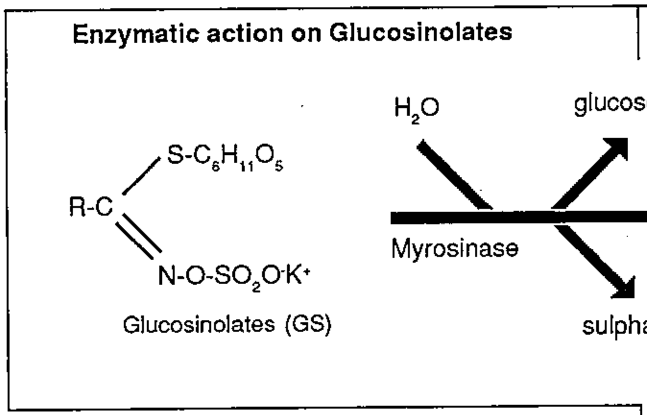

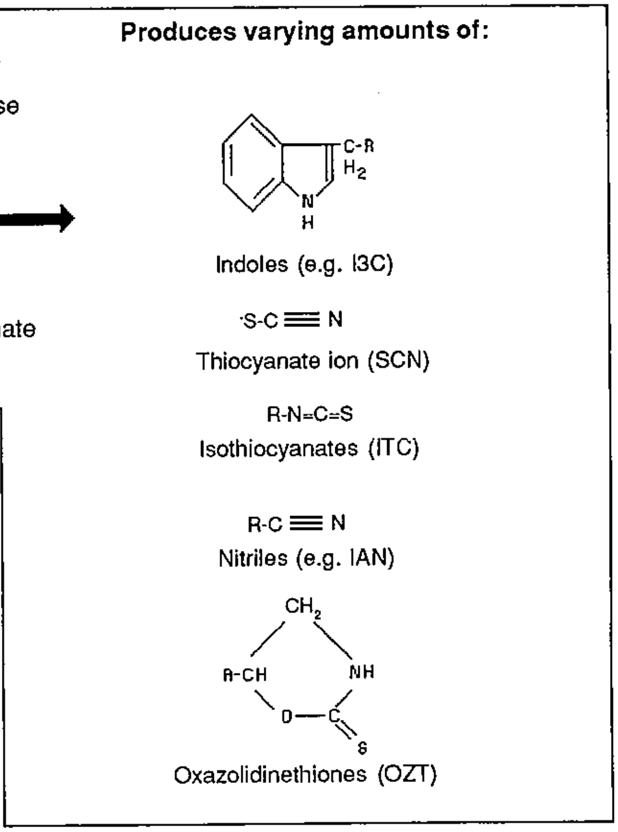

FIGURE 1. The enzymatic formation of active Glucosinolate compounds in members of the *Cruciferae* family. [R=side chains]

mary tumors in rats when given before or after carcinogen exposure,*(11,12)* while phenethyl-ITC given before prevents mammary, lung and forestomach tumors in rodents.*(11)* Cabbage and cauliflower reduced mammary tumor incidence in rats when fed after carcinogen administration.*(13)* As a consequence of some of these findings, in 1982 the National Research Council, Committee on Diet, Nutrition and Cancer, recommended the increased consumption of cruciferous vegetables to help reduce the incidence of cancer in humans.*(14)*

It must be remembered that most of these GS products are also goitrogens. Based on the use in the diet prior to this recommendation, consumption of greater amounts of these presents a reason for concern.*(15)* On the other hand, potential therapeutic utilization of these products for hyperthyroidism exists, especially in combination with other active botanical agents.*(16)* This also requires a specific understanding of their activity, availability and relative abundance in various plants and their component parts. For these reasons an overview of the research that investigates these points is in order and should be of interest to all.

Early studies on Brassica species

Cabbage was the first food discovered to cause goiter when it was used as part of the daily diet in a laboratory experiment on syphilis in rabbits.*(17)* This effect was soon confirmed by other investigators.*(18,19)* Winter cabbage was found to be more effective than summer cabbage. Steaming cabbage increased its activity. They also found the equivalent activity in steamed Brussels sprouts, cauliflower and turnips.*(19)* It was soon demonstrated that feeding rabbits additional iodine together with either raw or steamed cabbage prevented goiter formation.*(20,21)* By measuring radiolabeled iodine uptake by the thyroid of human volunteers, a variety of food plants were screened for their inhibitory effect. Raw rutabaga was the most consistent and potent inhibitor with raw and cooked turnips, cooked rutabaga and raw cabbage having positive but inconsistent results. Cooked broccoli and cauliflower were ineffective.*(22)*

Testing cabbage and turnips from different locales produced variable activity. Assuming that the active agent was a glycoside activated by enzymatic action, the seeds of different cruciferae were tested because of their consistently high glycoside content. Hyperplastic thyroids with no colloid were produced in rats fed seeds of white and black mustard that were steamed and unsteamed seed from cabbage and rape. Steamed rape seed was ineffective.*(23)* The seed from turnip, rutabaga and marrow-stem kale likewise produce hypertrophy and hyperplasia of the thyroid with no colloid. All *Brassica* seed thus tested was found to be active, but of particular interest was that iodine administered simultaneously did not prevent goiter formation.*(24)* The feeding of rape seed led to changes in the basophilic cells of the pituitary consistent with thyrotropic hormone synthesis.*(25)* Thyroid hyperplasia induced by these seeds rapidly regressed with removal of the pituitary in rats.*(26)* Production of thyroid hormone was therefore being depressed by factors in *Brassica* plants causing feedback stimulation to the pituitary to increase output of the thyrotropic hormone which resulted in goiter formation.

It became apparent that the concentration, activity and/or type of active constituents in these plants depended not only on the species of plant but its variety, where it was grown, the time of year grown and harvested, the processing, the part used and concomitant nutrition.

Though this is true for all types of plants the degree of variability exhibited by the *Brassica* plants was baffling and further investigations ensued. Of primary importance was identification of the "predominant active constituent."

Thiocyanates

Early studies suggested the goitrogenic activity was due to cyanide components and not SCN.*(27)* However in testing SCN as a means to control hypertension in humans several patients developed goiters that could be reduced by administering dessicated thyroid.*(28)* Subsequently, it was shown that SCN blocks iodide uptake by the thyroid, particularly when serum levels are low.*(29)* It prevents concentration of iodide by the gland, eliminating the gradient between it and the serum.*(30)* It appeared that its effects require a diet low, though ordinarily adequate, in iodide. But it has been shown that by being oxidized by lactoperoxidase it also helps prevent the oxidation of iodide to iodine, thus inhibiting organic iodations.*(31)*

SCN is derived from GS and occurs in *Brassica* vegetables in greater amounts than in other vegetables, with Brussels sprouts, cauliflower, savoy kale, turnips, cabbage, sauerkraut, kohlrabi and rape testing positive (listed in the approximate order of diminishing content).*(33,34,35)* The SCN content of these plants is much greater in the spring.*(36)* The greatest concentration of SCN in cauliflower and broccoli heads occurred at their premature stage of development, but relatively high quantities were found at the optimum mature stage. The 9 cauliflower cultivars tested had significantly more SCN than 6 broccoli cultivars with the exception of "Jet Snow" cauliflower which had much less.*(37)* Likewise, in marrow-stem kale and turnip rape SCN content was higher in early growth periods. Marrow-stem kale also showed a 3-fold higher content in its leaf than in the petiole or stem and 2-5 times the amount in young versus old leaves of the same plant.*(38,39)* The decreased iodotyrosine production and/or the inhibition of iodine uptake by marrow-stem and thousand-head kale was the same as that of their SCN content and reflected its relative presence.*(40)* However, the activity was different and greater in rape which has less SCN, indicating the presence of some other significant component.*(39,40,41)* The goitrogenic activity of cabbage is also not entirely due to SCN.*(42)*

Besides *Brassica* species, another cruciferous vegetable that contains significant SCN is the radish. Its root tissue yields more when planted in early spring, and its content is higher when grown in organic soil rather than loam.*(43)* Of those tested of the red type the root of Vick's Scarlet Globe contained the most SCN and Cavalier the least (1/2 as much). Of the white Burpee White had the most, and White Chinese (Celestral) the least (1/3 as much). The Round Black Spanish black type had a high content comparable to other types.*(44)*

Whereas SCN is normally formed as an enzymatic product of indole GS it has been shown in pepper cress leaves, gardencress seed and field pennycress to result from enzymatic cleavage of intermediate benzyl-ITC for the former and allyl-ITC for the latter, yielding benzyl-SCN and allyl-SCN, respectively.*(45,46)* These ITC are abundant in the CRUCIFERAE.

Isothiocyanates

Milk from cows in Australia grazing on such wild crucifers as pennycress and turnip weed was associated with an interference of iodine uptake.*(47)* Methylsulphonylpropyl-ITC derived from turnip weed was studied and found to be 40% as active as thiouracil in inhibiting iodine uptake by the thyroid in rats.*(48)* Other wild crucifers found in the pastures of goitrous areas of Tasmania yielded different ITC such as 3-butenyl-ITC in charlock.*(49)* One GS that is quite common in the CRUCIFERAE is sinigrin, which yields allyl-ITC. It occurs in far greater amounts than SCN in cabbage, for instance.*(50)* Besides allyl-ITC, 3-butenyl-, n-butyl-, methyl- and methylthiopropyl-ITC are also found in fresh cabbage,*(51,52)* though of these only the first 3 can be obtained enzymatically from dried cabbage.*(52)*

Oriental *Brassica* vegetables such as pak-choi,*(53,54)* Chinese cabbage*(54)* and kairan or Chinese kale*(53,54)* contain mostly 3-butenyl- and 4-pentenyl- ITC, while the Oriental mustard greens are very high in allyl-ITC.*(54,55)* Red cabbage has much more allyl-ITC than white, while cauliflower has little and turnip has none.*(56)* Of activated non-*Brassica* CRUCIFERAE, horseradish root is high in allyl-ITC *(57)* and radish root contains 4-methylthio-3-butenyl-ITC.*(58)*

Allyl-ITC was shown to significantly depress the iodine uptake in rat thyroids, similar to feeding them cabbage. Benzyl-ITC has also been found to be goitrogenic in animals.*(50)* Besides inhibiting inorganic iodide concentration in the thyroid, allyl-ITC and the less potent methyl- and butyl- ITC significantly depressed formation of diiodoty-

Scientific and common name	Plant part[a]	SCN[b]	ITC[c]						OZT[d]	Nitriles[e]						References
		I	A	Bu	MSB	MSP	P	PE	V	CEB	CEP	CHB	IAN	MCT	PPN	
B. oleracea var. *capitata* (Cabbage)	H	✦	✦			✦					✦		✦			8,15,34,35,51,52, 56,90,92-4,96,97
subv. *rubra* (Red cabbage)	H	✦	✦		✦	✦			✦							56,90,92,96,97
var. *italica* (Broccoli)	F	✧			✦								✦			8,15,37,90,91,92, 94,105,109
var. *botrytis* (Cauliflower)	F	✧	✦										✦			8,15,34,90,91,92, 106,109
var. *gemmifera* (Brussel sprouts)	H	✧	✦						✦				✦			8,15,35,90,91,92, 106,109
var. *fruticosa* (Kale)	L	✦											✧			8,108,109
var. *sabauda* (Savoy kale)	L	✧				✦										35,45,92,96,97
var. *alboglabra* (Chinese kale)	L			✦												53,54,94
var. *acephella* (Thousand head kale)	L	✦	✦	✦												39,40,49
subv. *plana* (Marrowstem kale)	L	✦	✦						✦							38,39,40,67,91,92
subv. *selensia* (Curly kale)	L	✦				✦										91
subv. *sabellica* (Collards)	L	✦	✦						✧				✦			8,91
B. gongyloides (Kohlrabi)	St	✦						✦								90,91,92,109
B. napobrassica (Rutabaga)	R	✦						✦	✧					✦	✦	15,45,65,90,93, 102,103,109,137
B. rapa (Turnip)	R	✦		✦			✦		✦						✦	15,54,65,66,67, 101,102,103,109
	L	✦		✧					✦				✧			8,35,54,67,101
B. juncea (Oriental mustard)	L		✧													54,55,91,93
	Se	✦	✧													56,91,93
B. nigra (Black mustard)	Se		✧													56
B. campestris var. *pekinensis* (Chinese cabbage)	H	✦											✧			8,54
var. *chinesensis* (Pak choi)	L			✦			✦	✦								53,54
var. *oleifera* (Turnip rape)	Se			✦			✦		✦	✦						67,113,114,115, 116,133,142
B. napus (Rape)	Se	✦		✦					✧			✦				60,65-67,93,111, 113-6,119,129, 141,142

TABLE 1. Main Glucosinolate hydrolysis products of cultivated *Brassica..*

Key to abbreviations:
a: F= *flowers*, Fr= *fruit*, L= *leaves*, R= *roots*, Se=*seeds*, St=*stems*
b: SCN= *thiocyanate*, A=*allyl*, B= *benzyl*, I= *ion*
c: ITC= *isothiocyanate*, A= *allyl*, B= *benzyl*, HB= *p--hydroxybenzyl*, MS= *methylsulfonylpropyl*, MSB= *4-methylsulfinylbutyl*, MSP=*3-methylsulfinopropyl*, MTB=*4-methylthio-3-butenyl*, P= *pentenyl*, PE= *phenylethyl*
d: OZT= *oxazolidinethione*, D= *5-dimethyl*, E=*ethyl*, M= *4-methyl*, Ph= *5-phenyl*, V= *(-)5-vinyl*, +V= *(+)5-vinyl*
e: BC= *benzylcyanide*, CEB= *1-cyano-3,4-epthiobutane*, CEP= *1-cyano-2,3-epithiopropane*, CHB= *1-cyano-2-hydroxy-3-butene*, CHE= *1-cyano-2-hydroxy-3,4-epithiobutane*, IAN=*indole-3-acetonitrile*, MCT=*4-methyl-1-cyanothiobutane*, PPN= *3-phenylproprionitrile.*

✦= predominant constituents for that plant.
✧= exceptionally high concentration compared to other plants.

Scientific and common name	Plant part[a]	SCN[b]			ITC[c]						OZT[d]					Nitriles[e]			References
		A	Be	I	A	Be	Bu	HB	MSP	MTB	D	E	M	Ph	+V	BC	CHB	CHE	
Cultivated:																			
Amoracia rusticana (Horseradish)	R				✧														57
Crambe abyssinica (Abyssinian kale)	Se														✧		✦	✦	77,116,118, 129,131
Lepidium sativum (Garden cress)	L					✦										✦			45
Raphanus sativus (Radish)	R			✦						✦									15,43,44,58, 90,93
Sinapis alba (White mustard)	Se							✦											61
Wild:																			
Barbarea vulgaris (Winter cress)	Se													✦					78
Coringia orientalis (Hare's ear mustard)	Se										✦								62
Lepidium ruderale (Pepper grass)	L/Se		✦																45,46
Rapistrum rugusum (Turnip weed)	Fr/L								✦										48,49
Sinapsis arvensis (Charlock)	L						✦												49
Sisymbrium austriactum (Wild mustard)	S										✦		✦						76,120
Thlaspi arvense (Field pennygrass)	L/Se	✦																	46,57

TABLE 2. Main Glucosinolate hydrolysis products of some cultivated and wild non-*Brassica* cruciferae.

Key to abbreviations:

a: F= *flowers*, Fr= *fruit*, L= *leaves*, R= *roots*, Se=*seeds*, St=*stems*
b: SCN= *thiocyanate*, A=*allyl*, B= *benzyl*, I= *ion*
c: ITC= *isothiocyanate*, A= *allyl*, B= *benzyl*, HB= *p--hydroxybenzyl*, MS= *methylsulfonylpropyl*, MSB= *4-methylsulfinylbutyl*, MSP=*3-methylsulfinopropyl*, MTB=*4-methylthio-3-butenyl*, P= *pentenyl*, PE= *phenylethyl*
d: OZT= *oxazolidinethione*, D= *5-dimethyl*, E=*ethyl*, M= *4-methyl*, Ph= *5-phenyl*, V= *(-)5-vinyl*, +V= *(+)5-vinyl*
e: BC= *benzylcyanide*, CEB= *1-cyano-3,4-epthiobutane*, CEP= *1-cyano-2,3-epithiopropane*, CHB= *1-cyano-2-hydroxy-3-butene*, CHE= *1-cyano-2-hydroxy-3,4-epithiobutane*, IAN= *indole-3-acetonitrile*, MCT=*4-methyl-1-cyanothiobutane*, PPN= *3-phenylproprionitrile*.

✦= predominant constituents for that plant.
✧= exceptionally high concentration compared to other plants.

rosine and even more the iodothyronines in rat thyroid lobes *in vitro*. These effects occurred at a concentration lower than that which blocks thyroid iodide uptake, or in the reverse order of the dual effect produced by SCN. However, the instability of ITC in water may reduce the potency of their *in vivo* effects.*(59)*

Most *Brassica* seeds contain large amounts of allyl-ITC, including black mustard, cabbage, cauliflower, Brussels sprouts and savoy kale.*(56)* Turnip and rape seeds contain mostly 3-butenyl-ITC.*(56,60)* The goitrogenic p-hydroxylbenzyl-ITC *(50)* predominates in white mustard seeds *(Sinapsis)*.*(61)* Most of the 43 wild Scandinavian non-*Brassica* crucifers were shown to have large quantities of a variety of ITC in their seeds, but 10 species had none.*(57)* An important discovery concerning anti-thyroid activity of certain ITC came when the seeds of a wild Canadian species were analyzed.

Oxazolidinethiones/goitrin

Hare's ear mustard is a common weed in the wheat fields of western Canada and has intensely bitter tasting seeds. It was discovered that its bitter taste was due to a GS that contains an unstable hydroxyl group which cyclizes immediately after hydrolysis. This product was identified as 2-mercapto-5,5-dimethyl-oxazoline (5,5-dimethyl OZT).*(62)* When comparing it to thiouracil in inhibiting thyroid gland function in rats it was found to be 40% as effective.*(63)* In humans its demethylated form was 75% as effective as thiouracil.*(64)* So, it was met with great excitement when a similar cyclized compound (from 2-hydroxy-3-butenyl-ITC) was discovered in rutabaga and turnip root and in larger quantities in the seeds (listed in the order of highest content) of kale, rutabaga, rape, broccoli, cabbage, kohlrabi, turnip, Brussels sprouts and Chinese cabbage. It was identified as L-5-vinyl-2-thiooxazolidone and it equalled the activity of 6-n-propyl-thiouracil and thiouracil.*(65,66)* It has since been designated as 5-vinyl-oxazolidinethione (5-vinyl-OZT) or goitrin.

Further studies found goitrin in the green parts of rape, turnip rape, turnip, marrow-stem kale and rutabaga.*(67)* These had been fed to cattle in areas of Australia high in goiter in spite of iodide supplementation, so the transfer of OZT to milk was suspected.*(47)* However, since marrow-stem kale seeds and leaves contained ITC in addition to 5-vinyl-OZT and wild pasture crucifers were also high in ITC the complete cause could only be surmised.*(49)* An analysis of fresh cabbage leaves of 7 varieties for goitrin yielded small amounts that seemed relatively insignificant.*(68)* But the population of Carpathian Ruthenia of the 1920's who lived on practically nothing but cabbage were quite goitrous. The incidence of thyrotoxicosis decreased and goiter increased in Belgium during World War II when the population was forced to eat a diet high in cabbage and turnips. Also during the war the monks in a Belgian monastery all developed goiters when forced to subsist on a diet of rutabagas and tulip bulbs.*(69)* Yet, a story was circulated about an herbalist in Ontario who was evicted by local medical authorities for advocating the use of turnips in the treatment of hyperthyroidism.*(70)*

Studies showed that whereas cabbage goiter can be prevented by supplementing iodine in the diet this does not prevent *Brassica*-seed goiter due to OZT. Also, heating or boiling the intact plant tissue destroys its activity, but if it is ground and exposed to water for several minutes first, the activity is not completely destroyed by boiling or evaporation. This is because heat destroys the activating enzyme, but not the active OZT. Alcohol also destroys the enzyme activity.*(69)*

The glucosinolate from which goitrin is derived was identified and named progoitrin. It is enzymatically converted to L-2-hydroxy-3-butenyl-ITC which cyclized to 5-vinyl-OZT.*(71)* This goitrin from *Brassica* roots and seeds is exclusively of the levorotatory configuration.*(72)* It was assumed that cooking the *Brassica* sources of this compound prior to consumption would prevent the conversion of the inactive progoitrin and thus block the production of the active goitrin.*(73)* However, it was shown that feeding pure progoitrin (0.5-2.0 gm, equivalent to 165-670 mg goitrin) greatly decreased iodine uptake in euthyroid humans (ranging from 6-65% of the original uptake). In a thyrotoxic patient given 2 gm, it reduced the uptake to 14% of the original. A patient with fairly severe recurrent Grave's disease was given 1 gm progoitrin orally once daily for 6 weeks. 24 Hour radiodine uptake was decreased by 50% (the same as with propylthiouracil) with a progressive fall in basal metabolic rate (BMR) and protein bound iodine (PBI) and a gradual increase in body weight. Whereas goitrin reaches its maximum concentration in the serum 4 hours after oral administration, progoitrin reaches its maximum in 35 hours. This may explain why purified goitrin causes nausea and vomiting within a few hours while oral progoitrin produces no ill effects. After progoitrin is administered it takes 4 days for the derived goitrin to be eliminated in the urine. In rats oral progoitrin doses below 1 gm were more effective than those given parenterally.*(74)* The explanation of this conversion of progoitrin to goitrin in the body became apparent when it was demonstrated that common enteric organisms (e.g. E. coli) were able to hydrolyze the precursor and thereby activate it.*(75,76)* Parenterally administered progoitrin may undergo enterohepatic circulation to expose it to these bacteria. Antibiotic (i.e., amphotericin B and neomycin) administration blocks the conversion of progoitrin to goitrin in the gut. The hydrolytic activity of rat fecal bacteria is less than that in humans.*(76)* This helps explain early studies in animals where cooked *Brassica* vegetables were less active or inactive. Problems with progoitrin include its short shelf life (1-2 weeks), but if kept in a desiccator it remains intact for 2-3 years. Its failure to appear in commercial production is due in part to the problem of obtaining exclusive patent rights.*(70)*

Both optically active forms of goitrin have equal antithyroid effects, possessing 2% of the potency of propylthiouracil in the rat and 133% of its potency in humans.*(76)* Though L-goitrin is derived exclusively from *Brassica* species, it was discovered that R-goitrin could be produced from commercial Abyssinian kale (Crambe) seeds and its GS epi-progoitrin.*(77)* Besides the aforementioned Hare's ear mustard, other wild crucifers that have GS with hydroxy groupings that on hydrolysis spontaneously cyclize to form active OZT include wild mustard (4-methyl-OZT) and winter cress (5-phenyl-OZT).*(76)* The seeds of winter cress contains ITC in addition to OZT.*(78)* Its 5-phenyl-OZT has only 1% of the antithyroid activity of propylthiouracil in the rat, but 75-100% of its activity in humans, or about 50% of the activity of goitrin.*(79)* One reason these hydrolyzed compounds are less potent in rats is the way they are metabolized. Rats convert much of administered goitrin to its 4-hydroxy metabolite which has less activity.*(80, 81)*

The process of determining dosage for humans then must be done independently of animal research. The rate coefficient of radioiodine uptake in humans gradually decreased in relation to the administered dose of goitrin, with 80% after an administration of 25 mg to 45% after 400 mg.

Repeated administration with its potential for accumulation of the active goitrin could significantly alter these figures.*(82)* In studying the mechanism of goitrin activity it was found that it has no effect on iodine absorption from the GI tract in chicks but acts primarily on the thyroid gland.*(83)* The thiol resonance form of goitrin allows it to be iodinated in preference to tyrosine by thyroid peroxidase or to induce changes in the enzyme.*(84)* In chicks injected or fed orally with goitrin the iodination of tyrosine, the synthesis of iodothyronines and plasma levels of thyroxin were decreased, with the only difference between goitrin and propylthiouracil being the slightly longer latent time and little faster attenuation of the former.*(85, 86)*

In the rat thyroid *in vitro* goitrin weakly inhibited MIT formation but strongly inhibited DIT formation.*(87)* *In vivo* intrastomach injection of goitrin in the rat for 7 and 14 days induced hypothyroidism by inhibiting the coupling reaction of iodotyrosine residues into iodothyronine.*(88)*

Additive effects and plant variations

The identification of at least 3 different types of active constituents in cruciferous plants raises the possibility of synergism of their relative activities.*(82)* To study this SCN (1 mg), allyl-ITC (2 mg) and goitrin (50 mcg) (amounts present in a daily cabbage ration) were administered orally alone or in combination to rats for 21 days. When the syntheses of iodoamino acids were compared it was found that the combination of three was more inhibitory than combinations of two or any one given individually. The total quantity of iodothyronines (T3 and T4) formed was decreased to a high degree of statistical significance in all groups compared to controls. Groups fed one compound had a mean value of 15% whereas groups fed with two or three compounds had a mean value of only 10% compared with the control group with 24% iodothyronines. Thyroid weight was increased by all compounds singly or combined.*(89)*

The combined effects of these active constituents makes their relative presence in different *Brassica* significant. The difficulty in assessing these differences arises from the variability between different cultivars of the same species. For example, the Rapine cultivar of the broccoli variety contains OZT, is high in ITC and low in SCN, whereas Premium and other broccoli cultivars have no OZT, are low in ITC and high in SCN. But in most other varieties specific tendencies were evident. White cabbage cultivars tend to be high in SCN and low in OZT, whereas red cabbage generally has more OZT than white. Kohlrabi and red and white radish cultivars are more consistent, but contain little SCN and ITC and no OZT. Wheras rutabaga cultivars are high in OZT and ITC and low in SCN, cauliflower is just the opposite.*(90)*

Brussels sprouts are consistently very high in SCN in 2 studies but one shows significant ITC and OZT content while the other does not, even for the same Jade Cross I cultivar.*(90,91)* Whereas the kale subvarieties curly and marrow-stem are low in all 3 categories, collards are high in all 3, especially OZT. Oriental mustard greens are high in ITC and low in SCN and OZT. So every conceivable combination is represented. Even different cultivars of the same plant variety often show differences in the amount and types of GS that they contain.*(91)* Further, the different parts of the same variety of species differ in their content.*(92, 93)* But in general, for the purpose of distinguishing antithyroid versus anticancer effects, OZT is found more commonly in the seeds and roots while SCN and its indole counterparts are more common in the leaves and flowers (or heads of either). Different ITCs occur throughout the various parts of cultivated *Brassica* plants.*(91,92,93,94)* These patterns hold true for the seeds of wild *Brassica* species as well *(95)* but their leaves have little SCN, while total GS levels were higher than cultivated *Brassica. (94)*

Special considerations for various CRUCIFERAE *products*

In analyzing over 80 cultivars of cabbage, wide variations occurred for all predominant constitutents.*(96,97)* Larger heads have a lower GS concentration. Savoy cabbages are highest in SCN yield, while red gives the most OZT and white has the most allyl-ITC. Market cultivars are higher in SCN and methylsulfinylbutyl-ITC and lower in allyl- and methyl-sulfinylpropyl-ITC than cultivars for storage or kraut. Kraut cultivars are highest in total GS;*(97)* however, after fermentation the kraut contained no OZT or ITC, only SCN.*(98)* Storage cultivars undergo fluctuation after harvest with all 3 types of GS products showing an increase after 5 1/2 months and a decrease after 7 months of storage.*(99)* While the seeds of 50 cabbage cultivars contain 10-fold more GS than the heads, they have relatively less SCN and more goitrin.*(100)*

Over 20 turnip rape cultivars had roots containing more OZT, SCN and total GS than the tops. The total GS in the seeds are 30-110 times those in the vegetative parts and correlate to the pattern of the tops.*(101)* Of the 31 turnip root cultivars Yellow Purple Top Aberdeen was very high in ITC, SCN and OZT whereas Hybrid Petite White had no goitrin, low SCN but equally high ITC. GS products generally increase with maturity of the root.*(102,103)* Predominant GS products also change during root development: SCN at 2 weeks, ITC at 4 weeks and goitrin at 6-8 weeks (marketing stage). Total GS is 38% greater in turnips grown on organic versus loam soil.*(104)*

Rutabaga roots contain more GS than turnips but show the same developmental variation. They have 15% more GS when grown on organic rather than loam soil.*(104)* In the 25 rutabaga cultivars studied, the OZT content was usually greater than for turnips, with E. Laurentian Purple Top being the greatest. SCN content was somewhat less than turnips, being lowest when the plant was seeded early, while the ITC content was comparable to turnips.*(102,103)*

Broccoli has the highest variability of *Brassica* vegetables. Ten different breeding lines showed GS content reflecting amounts of OZT and ITC from very high to very low, and SCN levels that were high to low in multiple combinations.*(105)* Brussels sprouts, high in SCN and variable in OZT and ITC,*(91)* were found to be more bitter in cultivars that are high in the GS producing allyl-ITC and goitrin.*(106)* However, when cooked the antithyroid activity was destroyed. This was demonstrated when 150 gm/day was fed to 10 volunteers for 4 weeks and no change in thyroid function was produced.*(107)* It was shown that boiling destroyed 35-50% of the GS. Volatile ITC (such as allyl-ITC) disappears completely and goitrin is partially degraded by boiling.*(108)* A study of the effects of cooking on green and red cabbage, Brussels sprouts, kale, cauliflower, broccoli, rutabagas, kohlrabi and turnip showed that the SCN source was also reduced by about 1/3 and 10-30% of all GS goitrogenic products were leached into the cooking water.*(109)*

Since CRUCIFERAE seeds contain the highest concentration of goitrogenic GS, particularly progoitrin, an abundant amount could be supplied from the meal of crucifer oil seed crops, i.e., rape, turnip rape, Abyssinian kale, Oriental mustard and white mustard.*(110)* In fact, these seed oils have been produced and used for centuries in India and more recently in Northern Europe and Canada. While oriental mustard is characterized by high allyl-ITC, rape and turnip rape seed meals are high in OZT and other ITC.*(111,112,113)* Rape is 3 1/2 times higher in OZT than turnip rape.*(112-116)* While cabbage seeds can also have a high content of both GS products OZT and ITC , they, like turnip rape seeds, contain a complex variety of ITC not found in rape seeds.*(111,117)* Abyssinian kale (Crambe) seed meal, like rape seed meal, produces large amounts of goitrin (10-13 mg/gm versus 8-14 mg/gm respectively), though its spacial configuration is (R) rather than (S).*(77,113,116,118)* Also, it produces much less ITC than rape seed meal.*(116)* Kale seeds have some of the highest OZT content,*(66,91)* but with increased use of rape seed oil, known in this country as canola oil, the availability of this seed meal as an inexpensive source of goitrin is most promising.*(70)* However, programs to develop strains low in GS are being pursued to allow the meal to be more widely used as a source of livestock, and eventually human, protein.

Enzymatic influence and nitrile production

Thus far, the focus has been on the hydrolysis of glucosides which exist in all of the species of the mustard family. This enzymatic process resulting from maceration detaches the glucose moiety and the aglucones undergo a Lossen-type rearrangement resulting in their conversion to various weak ITC goitrogens. Also, 2 exceptional subsequent conversions have been emphasized. First, in the case of 3-indolmethyl GS (glucobrassicin), the intermediate skatyl-ITC undergoes further immediate hydrolysis at a neutral pH to release SCN ion and 13C condenses to 133', or at an acid pH forms IAN. Thus we have both weak goitrogenic and anticarcinogenic products from this GS. In the second case a GS with a hydroxy group in the gamma or beta position, for example 2-hydroxy-3-butenyl GS (progoitrin), on enzymatic hydrolysis produces a hydroxyalkyl-ITC which undergoes spontaneous cyclization to a 5-member ring, forming an OZT (in this case goitrin, a potent goitrogen).*(120)*

However, the studies that investigated these reactions were based upon deactivating endogenous enzymes by heating and then catalyzing the hydrolysis with the enzyme myrosinase (now known as thioglucoside glucohydrolase), which is derived from white mustard powder, since this was believed to be the activating enzyme in all cruciferous species. In rape seeds or seed meal heated to 90°C for 15 minutes, endogenous myrosinase remained active with 4% moisture but was inactivated at this temperature by moisture levels of 6.4-8.4% whereas the GS for ITC and OZT were not heat labile under these conditions.*(116)* Other studies have shown myrosinase is deactivated by alcohol as well.*(76)* Nearly total conversion of GS to ITC and OZT by added myrosinase occurred in 30 minutes. Optimum formation of ITC took place at pH 6-9 and OZT at pH 7-9, while both yielded most at 70°C and in the presence of ascorbic acid.*(116)* Ascorbic acid acts not as a coenzyme but as an immediate activator of myrosinase, yet it actually accelerates its heat inactivation. *(121)* It activates one type of myrosinase but not all forms of this enzyme so its relative effect depends on whether whole mustard flour is used.*(122)*

An interesting development occurred when it was discovered that the myrosinases from cabbage and mustard had different levels of activity based upon intrinsic differences or relative affinities.*(123)* Immunoelectrophoretic analysis of myrosinase from *Brassica* versus *Sinapis* species showed taxonomic differences.*(124)* It was shown by chromatography that the myrosinase from Oriental mustard seed produced 2 peaks *(125)* and that 4 separate glycoproteins had myrosinase activity, with 3 of these having remarkable molecular weight, sedimentation, chromatographic and electrophoretic resemblances.*(126)* Ultimately, 14 myrosinase isoenzymes were separated from a crude extract of white mustard. Several other isoenzymes were discovered for black mustard and rape seeds, each of the 3 species having their own characteristic pattern.*(127)* The two isoenzymes from rape seed functioned optimally at pH 4.4 and 8.0 with goitrin the sole product from pH 5.4-8, but the nitrile 1-cyano-2-hydroxy-3-butene was additionally produced from pH 5.4-2.6, being the major product below pH 3.8.*(128)* Preferential formation of goitrin over the nitrile with autolysis (endogenous enzyme hydrolysis) of the seed meals of rape and Abyssinian kale is increased by increasing the temperature by dry heating over 70°C and then by adding water at an alkaline pH. Otherwise the nitrile is preferentially formed by autolysis (80% to 20% goitrin) in the first minute.*(129)*

Similar to their seeds, the leaves of rape and Abyssinian kale when dried and treated with white mustard myrosinase at pH 5.0-5.8 gave goitrin but when crushed fresh and allowed to autolyze at the same pH the products were 3 nitriles: the 1-cyano-2-hydroxy-3-butene and diastereomeric isomers of 1-cyano-2-hydroxy-3,4-epithiobutanes.*(130)* A protein was isolated from Abyssinian kale seeds that prevents hydrolytic production of the former and promotes formation of the latter.*(131)* This epithiospecifier protein has also been isolated from turnip rape.*(132)* 1-cyano-3,4-epithiobutane is a major product of turnip rape seeds unless they are heated to 115°C for 30 minutes before hydrolysis. *(133)* Chinese cabbage seeds also contain this latter autolytic nitrile derived from 3-butenyl-GS.*(134)*

Nitriles constitute a significant portion of the components from vegetative parts of these plants. Volatile nitriles were higher in the macerated buds than leaves of rape and turnip rape.*(135)* Autolysis of fresh cabbage and Brussels sprouts gave a preponderance of nitriles over related ITC and goitrin, whereas the latter were formed more if air-drying occurred before autolysis. A wide variety of nitriles was formed from GS sources of ITC in cabbage and one was found in sauerkraut.*(136)* In rutabagas autolysis was shown to effectively reduce the quantities of ITC and especially goitrin when compared with freeze-dried samples that were hydrolyzed, with SCN ion remaining the same.*(137)* 1-cyano-4-methyl-thiobutane and 3-proprionitrile are the most prominent nitriles produced in rutabaga root,*(103,137)* while the latter predominates in turnip roots.*(103)* Lists of the major enzymatic products of GS from *Brassica* vegetables *(Table I)* and other CRUCIFERAE *(Table II)* are provided to summarize, simplify, and facilitate comparisons of those parts most commonly used.

Toxicity of crucifer sulfur-containing compounds

The reduction of nitrile production is important not only if one wishes to retain goitrin and ITC activity, but also because nitriles (as shown by those obtained from Abyssinian kale seed meal) are eight times more toxic than goitrin as demonstrated in mice.*(138)* In rats, R-goitrin caused hyperplastic goiter and some enlargement of the liver with mild cellular degeneration; the serum chemistry changes were small and included increased triglycerides and cholesterol, total protein, albumin and calcium and decreased serum urea and thyroxine.*(138,139)* S-goitrin in rapeseed meal showed reduced thyroid colloid but no liver toxicity in rats at doses comparable to those of semisynthetic R-goitrin that produce these effects.*(140)* On the other hand, rats receiving meal containing nitriles had enlarged livers with bile duct hyperplasia, fibrosis and megalocytosis of hepatocytes. The kidneys were also enlarged with lesions in the tubular epithelium, but the thyroids appeared normal.*(138)*

In animals, ruminants have the greatest resistance to the influence of compounds in rapeseed meal, especially the goitrogenic factors, since OZT is partly destroyed in the rumen. In swine rapeseed meal as over 4% of the diet increased the size of the thyroid and decreases suckling pig growth, maturation rapidity, food consumption, and lactation.*(141)* Poultry have repressed thyroid activity and a reduced growth rate, food intake and egg production.*(141;142)* Liver hemorrhage is another toxic effect in fowl *(142)* and is associated with the consumption of intact GS.*(143)* This only occurs when the GS is taken as components of rapeseed meal, implicating the associated nitriles. This hemorrhage can be reduced by taking supplemental vitamin K.*(144)* Even when no macroscopic lesions could be found in chicken livers, evidence of hyperplasia and increased plasma alkaline and transaminase activity suggested liver damage. Rapeseed meal also increased plasma total protein, albumin and cholesterol and decreased urate,*(145)* similar to the effects of R-goitrin on rats (139). Therefore, the use of these substances should be avoided where there is prior liver damage or hypercholesterolemia.

R- and S-goitrin given orally or IM in a single dose produced no embryopathic effect when given early in pregnancy to rats.*(146)* However, in golden hamsters, orally administered goitrin retarded fetal development and caused fetal death though no teratogenic effects were produced. *(147)* None of the sulfur-containing compounds tested (GS, ITC, OZT, or nitriles) were teratogenic to the rat fetus. But 3-methylsulfinylpropyl- and allyl-ITC as well as 1-cyano-3,4-epithiobutane all caused embryonal death and decreased fetal weight. S-1-cyano-2-hydroxy-3-butene also caused significant loss in fetal weight.*(148)* Therefore, the therapeutic use of these substances should be avoided in pregnancy.

Inadvertent toxicity involving the antithyroid effects may result from consumption of milk that contains these goitrogens. Use of *Brassica* fodder by cows increased the SCN level in milk by 300% and decreased the milk iodine level by 38%,*(149)* but its effect is relatively insignificant and may be controlled by iodine supplementation.*(45)* Yet endemic goiter occurred in Australia in areas where iodine was supplemented as milk cows were fed marrowstem kale and pastures contained cruciferous plants high in goitrogenic ITC.*(48,49)* However, OZT content has caused the greatest concern. While several studies show the transfer of OZT to milk in cows to be negligible or insignificant,*(150,151)* milk from endemic goiter districts of Sweden and Finland contained OZT levels high enough to be a causative factor *(152,153)* Wild Scandinavian crucifers are also high in ITC.*(57)* Both goitrin and the active 5-OZT are found in cruciferous weeds in Finland and with long term use cause goiters at levels far below those required to produce a decrease in a single radioactive iodine uptake test (154). About a 0.1% transfer of goitrin occurs from rapeseed extract cakes to milk, which can be significant in the milk of cows that are given this as supplemental feed (707 mcg/l milk at 3.9% of total feed).*(155)* Since as little as 100 mcg of goitrin taken orally for 5-6 months by human adults reduces serum thyroid levels,*(156)* this suggests that the use of therapeutic quantities of these goitrogens should be avoided in nursing mothers.

SCN when given in doses of 0.3 gm caused weakness, fatigue, nausea, vomiting, dizziness and reduced blood pressure in some humans who were being treated for hypertension.*(28)*

Summary and conclusions

The regular use of cruciferous vegetables for their indole GS products as part of a diet to avoid the development of certain types of cancers is appropriate if several parameters are followed. The presence of GS sources of SCN ion in these vegetables is correlated with their anticancer indole components. High ITC levels can also occur concomitantly. So a supplemental source of iodine is necessary to help insure against their blocking iodide uptake by the thyroid and resultant goiter formation. Without the additional iodine simple thyroid hypertrophy is the body's response to provide adequate uptake and thyroxin production. Prior mechanical processing, e.g. by cutting or grating as in cole slaw, induces an autolytic breakdown of goitrogens and anticarcinogens while cooking destroys some GS goitrogenic products and boiling leaches out more in the water but does not reduce the indole components. There is great variability within the *Brassica* genus and even between cultivars of the same species regarding the relative content of the GS products SCN, ITC and the more potent OZT (goitrin) which makes quantifying their amounts impossible for a review of this scope. But generally, those vegetables highest in goitrin that would have the greatest potential for inducing iodine-immune antithyroid activity include rutabagas, turnips, collards, red cabbage and Brussels sprouts.

Though low in SCN ion and indole GS products, an extract of certain CRUCIFERAE (especially *Brassica*) seeds is the best means of producing a concentrated product for those interested in using the antithyroid compounds therapeutically. These provide both goitrin, which blocks organic binding of iodine by the thyroid, and ITC, which though less potent has the same effect and also (like SCN) blocks the inorganic iodide 'pump' of the thyroid that concentrates this element in the organ. Since commercial canola oil production in this country is increasing, a supply of rapeseed, which has one of the greatest OZT contents and contains both ITC and SCN, should be readily available. If simple autolysis of the GS is preferred, the defatted seed meal is preheated to 70-120°C with dry heat for hours and the conversion to goitrin optimized in water at 70°C with an alkaline pH. The GS product is then extracted and concentrated, e.g. by freeze-drying the extract. But to maximize goitrin and ITC content and eliminate toxic nitrile contamination due to autolysis, the endogenous enzymes should be deactivated by moist heat (90°C for 15 min.) before mechanical processing. GS can be effectively extracted from either ground Crambe or rapeseed with a 1:3 mixture of water to acetone, methanol or ethanol. After removal of the oil and the organic solvent, purified myrosinase from white mustard is added to the aqueous extract with ascorbic acid at 70°C and a pH of 7-9. This activated extract could also be freeze-dried to concentrate and preserve its components. If one wished to utilize the iodide pump blocking activity of the ITC and SCN to increase the overall effect, an iodine restrictive diet could be employed to enhance this. The safe use of these substances can be assumed if the nitrile content is low and contraindications are recognized. Combined with other botanical products that are both antithyroidal and antigoitrogenic by reducing the production and/or activity of thyroid stimulating hormone, Graves' IgG and thyroxin (as covered in part I of this article *(16)*), an effective formula could be developed that would provide a therapeutic option in the management of hyperthyroidism.

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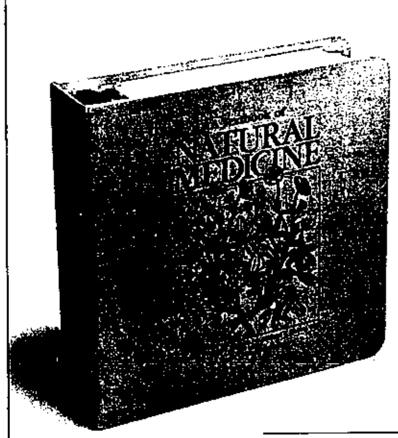

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