conferences, workshops, meetings and symposia. As one of the initial activities of the chapter, the Chemistry Department of University of Delhi is organizing an International Symposium on Green Chemistry in January 2001.

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REVIEW ARTICLES

Cancer modulation by glucosinolates: A review

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Glucosinolates (GLS) are a group of plant thioglucosides present in plants of Cruciferae family. They are well known for their toxic effects (mainly as goitrogens) in both man and animals at high doses. In contrast at subtoxic doses, their hydrolytic and metabolic products act as chemoprotective agents against chemically-induced carcinogens by blocking the initiation of tumours in a variety of rodent tissues, viz. liver, colon, mammary gland, pancreas, etc. They exhibit their effect by inducing Phase I and Phase II enzymes, inhibiting the enzyme activation, modifying the steroid hormone metabolism and protecting against oxidative damages. Acid condensation products (like DIM) are more effective than their parent compounds (like I3C). Anticarcinogenesis caused by GLS is reviewed here.

GLUCOSINOLATES (GLS) are a group of plant thioglucosides found among several vegetables. The first crystalline glucosinolate, sinalbin, was isolated from the seeds of white mustard in 1831. Since then, more than 100 different GLS have been characterized. GLS occur mainly in the order Capparales, principally in the families Cruciferae, Resedaceae and Capparidaceae, although their presence in other families has also been reported[1]. Some economically important GLS-containing plants are white mustard, brown mustard, radish, horse radish, cress, kohlrabi, cabbages (red, white and savoy), brussels sprouts, cauliflower, broccoli, kale, turnip, swede and rapeseed[2]. GLS concentration in plants depends on various factors such as variety, cultivation conditions, climate and agronomic practices. Concentrations in a particular plant also vary between different parts of the plant[3]. A considerable amount of research has been conducted to elucidate the toxic effects of GLS in animals. The ingestion of large amounts of GLS-containing feeds may reduce feed intake, cause thyroid gland hypertrophy and reduce levels of circulating thyroid hormones, mainly by inhibiting the iodine uptake by the gland[4–10]. Such effects may adversely affect the productive performance of livestock. Poultry and pigs are more susceptible than cattle,

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sheep and goat because the latter group of animals can detoxify GLS hydrolysis products to some extent. Many experiments have suggested that GLS can act as potent inhibitors of the toxic and neoplastic effects of a wide variety of chemical carcinogens. In this field, research is mainly conducted on laboratory animals (recently with volunteer human beings) to know in detail the operating mechanism, so that the knowledge can be applied for prevention of cancer in human beings. Our concern in this paper is to review the basic mechanism of anticarcinogenesis by GLS.

Chemistry of GLS and their breakdown products

The basic chemical structure of GLS consists of a thioglucose linked via a sulphonated oxime to a R group, where R may be aryl, alkyl or indolyl. Amino acids act as precursors of GLS biosynthesis in plants. Phenylalanine and tyrosine produce benzyl GLS and *p*-hydroxybenzyl GLS, respectively. Indole GLS are produced from D,L-tryptophan. GLS are not harmful as such, but are hydrolysed to various toxic products by the enzyme myrosinase. GLS and myrosinase coexist in the intact plant in separate compartments, but when the cell structure gets disrupted, they come in contact with each other. Thus, myrosinase hydrolyse GLS releasing glucose and an aglucone moiety, which may further undergo various rearrangements, producing isothiocyanate, thiocyanate, nitrile or other products like goitrin which are harmful. On the other hand, certain GLS metabolites are useful due to their protective effects against carcinogenesis.

Anticarcinogens of plant origin

Fruits and vegetables have been reported to contain a large number of potentially anticarcinogenic agents. These include allicin in garlic, isoflavones in soybean, lycopene in tomatoes, flavonoids in green and black tea, sulforaphane and other GLS in cruciferous plants, carotinoids in carrot, lignans in flax seed, etc[11–14]. However, GLS present in vegetables of Cruciferae family are widely regarded as potentially cancer-protective compounds. In order to understand the anticarcinogenic effect of GLS products, it is essential to have an overview of the process of carcinogenesis.

Common mechanism of carcinogen metabolism

Foreign compounds (such as toxic materials, carcinogens or others) after entering the body are metabolized as shown in Figure 1. The overall metabolism of foreign compounds is directed towards producing chemical species that can be excreted. Williams[15] has proposed two classes of enzyme system for the metabolism of xenobiotic compounds to excretory metabolites, which are termed Phase I and Phase II reactions. Sometimes, these foreign compounds lead to the formation of a tumour. The malignant form of tumour is known as cancer. The process of carcinogenesis is a multi-stage process in which at least three distinct phases can be recognized, viz. initiation phase, promotion phase and progression phase. Initiation is the genetic event, which comprises two distinct steps, viz. induction of the molecular lesions and fixation of these by DNA replication. The ultimate carcinogenic forms of carcinogens are charged electrophiles which are highly reactive towards DNA molecules. They bind covalently with DNA to produce DNA adducts. Such type of DNA modification is generally the major driving force for cancer development. The ability of carcinogens to exert their effects depends largely on the balance between activating enzymes. Any change in this balance will result in a change in the biological effect[16]. Some carcinogens, termed as 'direct acting', exist in the electrophilic form or get converted to electrophiles in solution. Others require metabolic activation for their action (Figure 1).

Mechanism of anticarcinogenesis

In relation to our previous discussion, the suggested anticarcinogenic mechanisms of GLS hydrolytic products in mammals include induction of Phase I enzymes, inhibition of enzyme activation, induction of Phase II enzymes, modification of steroid hormone binding, scavenging of electrophiles and protection against oxidative damage[17–23]. However, the species-specific anticarcinogenic mechanisms for different compounds remain to be clearly defined. The specific inducing chemicals derived from GLS have been identified as indole-3-carbinol (I3C), indole-3-acetonitrile (I3A), diindolyl methane (DIM), ascorbigen (ASC), nitrile, 1-cyano-2-hydroxy-3-butane (Crambene), 1-isothiocyanato-3-(methyl sulfinyl)-propane (IBN, also known as Iberin), phenyl ethyl isothiocyanate (PEITC), 1-isothiocyanato-4-(methyl sulfinyl) butane (Sulforaphane), 1-isothiocyanto-4-(methyl sulfonyl) butane (Erysolin), etc.[24–28].

Induction of Phase I enzymes

Phase I reactions involve oxidation, reduction and hydrolysis reactions, thereby making xenobiotics more polar. The most important Phase I enzymes are cytochrome P450 (CYP) enzymes (mixed function oxidase system or MFO system). This is b-type cytochrome which binds carbon monoxide. The reduced cytochrome–carbon monoxide complex has an absorption

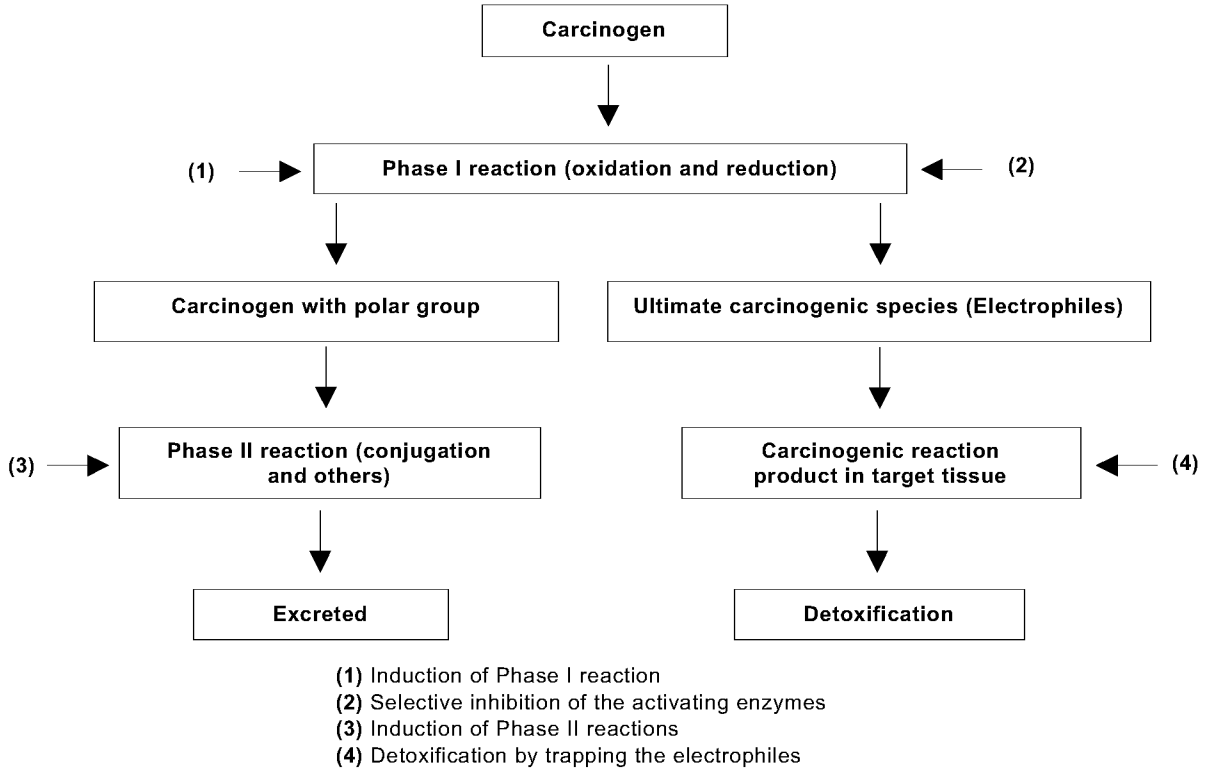

Figure 1. Common mechanism of carcinogen metabolism with the effects of inhibitors of carcinogenesis.

peak at 450 nm. The mechanism of action of MFO system is that the toxicant reacts with oxidized CYP, producing a complex which is further reduced by picking up hydrogen from the reduced flavoprotein, leaving the oxidized flavoprotein. This reduced complex subsequently reacts with molecular oxygen to produce water, reoxidized CYP and the hydroxylated toxicant which further undergo Phase II reaction and get excreted as water soluble metabolite[29]. CYP enzymes are products of the CYP super family of genes. Over a hundred mammalian CYP genes have been cloned and studied extensively[30]. Since CYP enzymes play key roles both in the activation of most carcinogens[31,32], as well as in the biotransformation of many important endogenous compounds and in the detoxification of numerous xenobiotics, a clear understanding of the properties of different CYP enzymes is essential. Table 1 presents some members of the CYP gene super family with their proposed function which are of interest to us.

CYP1A2 has 70–73% sequence identity with CYP1A1 in mammals and 96% in trouts[33] and both the enzymes are reported to be regulated by the same receptor, i.e. Ah receptor (Aromatic hydrocarbon receptor, regulates the expression of the UDP-glucoronosyl transferase, NAD(P)H:menadione oxidoreductase and glutathione transferase along with P_1 450 and P_3 450 genes)[34,35]. Though it is not clear whether due to this reason I3C was reported by some researchers[36] as a carcinogenic agent, it can be assumed that during induction of CYP enzymes, I3C may also induce the enzymes of the whole group which are recognized for their activating effect on carcinogens along with other detoxifying forms. Yang[37] reported that certain chemicals of dietary origin can inhibit the activities of these enzymes selectively, thus providing the opportunity for selective inhibition of the carcinogenicity or toxicity of known chemicals by specific inhibitors of CYP enzymes. Glucosinlates induce the CYP and thus help in excretion of carcinogens. The most dramatic increase in CYP effect has been reported with I3C and DIM and to a lesser de-

Table 1. Forms of cytochrome enzymes

Forms of Cyp	Proposed function	Refs
CYP1A1	Inducible member of CYP super family, helps in biotransformation of toxicant and carcinogen	34
CYP1A2	Catalyses the activation of carcinogenic aryl amino and AFB1	31, 75
CYP2E1	Catalyses the oxidation of many volatile environmental chemicals and anaesthetics	34, 44, 76–78
CYP3A4	Catalyses the biotransformation of many drugs	79, 80

gree with I3A (ref. 38). Many studies have been conducted to investigate the effect of GLS as Phase I enzyme inducers mainly in laboratory animals. In rodents, I3C induces CYP1A1 through its acid condensation products, which are produced non-enzymatically in the acid environment of the stomach[17,39]. It is also reported that though the I3C itself is a weak Ah receptor agonist and does not induce CYP1A1 by i/p injection, its acid condensation products are comparatively strong Ah receptor agonists[40] and potentialy induce CYP1A1 (refs 41 and 42). Guo *et al.*[43] stated that a single dose (100 μ mol) of phenyl isothiocyanate (orally) to male F344 rats caused marked increase in liver microsomal pentoxy resorufin *o*-dealkylase activity (10-fold) and the content of CYP protein (6.6-fold). Takahashi *et al.*[42] also found that I3C acid condensation products induce CYP1A (related all the isoenzymes of CYP1A group collectively) by trout embryo injection (21 days after fertilization) and by i/p injection to fingerling trout.

However, there are some variations in the mechanism of anticarcinogenesis. The points upon which all effects of anticarcinogenesis discussed in this review include experimental conditions, nature of GLS and carcinogen used, treatment regimen, target tissue examined, specific monooxygenase measured, dose of both carcinogen and anticarcinogen, timing of the treatment or pre incubation periods, etc.

Inhibition of enzyme activation

Most chemical carcinogens require metabolic activation before exerting their carcinogenic effect. Out of three major CYP forms in human liver microsomes, CYP1A2 catalyses the activation of carcinogenic aryl amines and aflatoxin B_1 (AFB_1), whereas the role of CYP1A1 in this is not yet certain[43,44]. Morse *et al.*[45] reported that in NNK [4-methylnitrosamino-1-(3-Pyridyl)-1-butanone, a potent tobacco carcinogen]-induced lung tumourigenesis, PEITC (Phenethyl ITC) is effective only when given prior to or during the NNK treatment, suggesting thereby that PEITC inhibits the activation of NNK. In another study, Takahashi *et al.*[46] used β-naphthoflavone (BNF), a known Ah receptor agonist and strong inducer of CYP1A in trout and mammals, to induce CYP1A in trout. They found that pre-feeding I3C or co-feeding I3C with a non-saturating dose of BNF (50 ppm) suppressed the inducing ability of BNF. From this result, they strongly suggested that I3C or I3C-derived compounds are inhibitors of enzyme activation. Researchers have reported that in rainbow trout, I3C is not an effective inducer of CYP1A-mediated AFB_1-9a-hydroxylase activity[17,47]. Whereas a reaction mixture (RXM) of I3C (produced in HCl to stimulate compounds generated in the low pH condition of the stomach) has shown to inhibit AFB_1–DNA binding *in vitro*[19]. Enzyme inhibition of AFB_1 activation by 3,3-diindolylmethane (DIM), the major low pH derivative of I3C found in trout liver, was reported by Dashwood *et al.*[48]. Takahashi *et al.*[46] have shown in the *Salmonella* assay with the trout liver S-20 activation system that DIM and RXM were inhibitory against AFB_1 mutagenicity. DIM, coinjected with AFB_1 into trout embryos, inhibited, both *in vivo* AFB_1–DNA binding and final tumour incidence, but I3C did neither[19,49]. These oligomers act as the alternative nucleophiles against the electrophilic toxicants[21,22].

Induction of Phase II enzymes

As shown in Figure 1, the anticarcinogenic effects of GLS hydrolytic products can also be mediated by induction of Phase II enzymes such as glucoronosyl transferase (GT), glutathione S-transferase (GST) and quinone reductase (QR). Phase II enzyme induction is a common feature of many chemoprotectants and the evidence is strong that Phase II induction before or during exposure to carcinogens can decrease or inhibit carcinogenesis[50]. Similarly, administration of ITC to rodents evokes a generalized electrophilic counter-attack response, characterized by the induction of Phase II enzymes and an increase in tissue glutathione (GSH) level[51–53]. Exposure of cultured cells and animal tissues to ITC leads to coordinated induction of these Phase II enzymes[54–56]. Active derivatives of GLS which are able to induce both phases of detoxification enzymes are already mentioned in this text. Crembene is a potent inducer of pancreatic and hepatic GSH at a dose of 30 mg/kg/day for 6 days[57]. It also induces pancreatic GST at subtoxic doses of 50–100 mg/kg/day for 7 days[58]. At these doses, it also induces the hepatic Phase II enzyme, GST and QR, with no effect on CYP1A activity[27]. Wallig *et al.*[59] had shown that crambene has a toxic effect on pancreas at doses of 200 mg/kg. Such induction of Phase II enzymes without concomitant induction of Phase I enzymes is termed as *monofuntional induction* and is thought to decrease the possibility of CYP bioactivated products attacking DNA, to cause mutations and ultimately cancer[60]. Benzyl ITC has shown to increase the activities of GST, NADP (H): Quinone Oxidoreductase and UDP Glucoronosyl transferase[61–65]. Dietary benzyl ITC increased the GSH level and level of glutathione S-transferase subunit-2 (of the α-class)[62–64]. The induction of GST has also been shown strongly by a GLS hydrolysis product, allyl ITC[66]. The presence of an α-hydrogen is required for the inductive activity of ITC[53]. Glutathione S-transferase has been studied extensively as a major detoxification enzyme. It catalyses the binding of a large variety of electrophiles to the sulfhydryl group of GSH[67,68]. Since the reactive ultimate carcinogenic forms

of chemical carcinogens are electrophiles, GST takes on considerable importance as a mechanism for carcinogen detoxification. Using a cyclocondensation assay, Zhang and Talalay[28] reported that many isothiocyanates are rapidly accumulated to high concentrations in a number of cultured mammalian cells. The magnitude of such accumulation is related to the specific ITCs, incubation temperature and cellular GSH content. They also found that Phase II enzyme inducer potencies of ITCs correlate with their levels of accumulation in Hepe 1c1c7 cells, which also suggests a possible mechanism for the differential potencies of these compounds in inducing both the phase enzymes. According to Zhang and Talalay[28], GSH negatively modulates the potencies of ITCs as inducers of Phase II enzymes, i.e. decreasing GSH levels in Hepa 1c1c7 cells increases the inducer potencies of ITC which can undergo conjugation with GSH, nonenzymatically and enzymatically. It is possible that GSH conjugation with ITCs is involved in their concentrative cellular accumulation. The changes in specific activities of GST and QR in the cytosols of several organs of mice and rats treated with various metabolites of GLS are given in Table 2. Induction of GST and QR has been expressed as ratios of specific activities of tissues obtained from treated and control animals[38]. The organs examined include liver, esophagus, forestomach, glandular stomach, colon, lung, kidney and bladder.

Scavenging of electrophiles

The scavanging of electrophiles by GLS hydrolysis products has already been discussed in the article.

Besides these four major mechanisms of anticarcinogenic function of GLS metabolites, two more mechanisms have been suggested which are discussed next.

Modification of steroid hormone metabolism

Studies have shown that oestrogens are metabolized by specific isozymes of P450. I3C-dependent induction of CYP1A2 mediates the effect of oestrogen 2-hydroxylase[69]. Since the formation of different oestrogen metabolites is linked to breast and uterine cancer, the use of I3C in woman has produced a beneficial effect through a modification of oestrogen metabolism. It seems apparent that I3C may be a very useful preventive agent against hormone-related cancers[20,70].

Protection against oxidative damages

One more mechanism suggested is protection against oxidative damage by GLS breakdown products[71–74]. It is well established that GLS breakdown products induce endogenous antioxidant defences such as UDP-glucuronosyl transferase in cells and *in vivo*. Plumb

Table 2. Induction of Phase II enzymes by isothiocyanates

Enzyme	R-NCS	Species	Tissue	Activity (treated/control)	Refs
GST	Benzyl-NCS	Mouse	Oesophagus	2.08–2.59	63, 81, 82
			Fore stomach	2.46	
			Liver	3.2	
			Small bowel	4.38–9.36	
			Fore stomach	3.43–4.29	64
			Liver	3–3.5	
			Kidney	1.35–1.37	65
			Small bowel	5.27–8.31	
			Colon	1.25	
	Allyl-NCS	Rat	Liver	1.26–2.25	66
	Phenylbutyl-NCS		Liver	1.35	61
	Sulforaphane	Mouse	Fore stomach	1.08–3	54
QR	Benzyl-NCS	Mouse	Fore stomach	2.57	64
			Liver	2.05	
			Lung	2.82	65
			Kidney	2.27	
			Small bowel	4.78	
			Colon	1.8	
			Bladder	2.41	
	Sulforaphane		Forestomach	1.05–3.1	55
	Phenethyl-NCS	Rat	Liver	5.1	43
	Phenylbutyl-NCS		Liver	1.44	61
	Naphthyl-NCS		Liver	2.23	83, 84

et al.[71] studied the free radical scavenging properties of representative extracts and of purified GLS from cruciferous vegetables and reported that GLS are unlikely to account for the direct antioxidant effects.

Conclusion and further scope

GLS hydrolysis and metabolic products have proven chemoprotective properties against chemical carcinogens. They block the initiation of tumours in a variety of tissues, e.g. liver, colon, mammary gland, pancreas, etc. They exhibit their effect by inducing Phase I and Phase II enzymes, inhibiting the enzyme activation, modifying the steroid hormone metabolism and protecting against oxidative damage. By inducing Phase I and Phase II enzymes they facilitate in detoxificiation of carcinogens. Some enzymes of Phase I reaction which are shown to activate the carcinogens, are inhibited selectively by glucosinolate metabolites. Acid condensation products (like DIM) are more effective than their parent compounds (like I3C). These oligomers act as alternative nucleophiles against the electrophilic carcinogen. They also inhibit AFB_1-activating enzymes as well as AFB_1–DNA adduction and thus prevent carcionogenesis by AFB_1. To avoid the activation by Phase I enzyme, only Phase II enzymes can be induced by monofunctional induction. Thus the basic concept of anticarcinogenesis has an influencive role for health awareness, encouraging the consumption of diet rich in fruits and vegetables, as well as for further studies which are necessary for successful application of the concept to protect cancer.

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