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Review

Diet-related cancer and prevention using anticarcinogens

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Compelling evidences indicate that dietary factors can contribute to human cancer risk and as such many of the cancers common in the third world countries and the western world, including liver, colon, prostate and breast cancers have been related to dietary behaviors. Dietary carcinogens identified to date include the mycotoxins, heterocyclic amines formed from heat treatment of meat, N-nitroso compounds and the polycyclic aromatic hydrocarbons. It has been recognized that diet-related cancers occur through an imbalance of carcinogenesis and anticarcinogenesis. Dietary anticarcinogens may therefore provide a means of retarding, suppressing or reversing the multi-stage carcinogenesis. An avalanche of dietary and plant-derived compounds has been reported to possess anticarcinogenic activities. Most of these agents possess intrinsic antioxidant, radical trapping and anti-inflammatory properties, which appear to contribute to their chemo preventive properties. Resveratrol, a phytoalexin, present in grapes, berries and peanuts and Curcumin the natural yellow pigment in turmeric isolated from the rhizome of the plant *Curcuma longa* elicit striking inhibitory effects on diverse cellular events associated with the process of carcinogenesis. Lycopene, a carotenoid present in tomatoes is a powerful quencher of singlet oxygen. Epidemiological evidence strongly suggests that lycopene consumption and tomato products contribute to prostate cancer risk reduction. Kolaviron, a natural biflavonoid antioxidant obtained from the seeds of *Garcinia* kola has been extensively investigated for it hepatoprotective, radical scavenging and antigenotoxic properties *in vitro* and *in vivo.* Each of these anticarcinogens alone or in combination could provide a sustainable chemopreventive intervention that might be useful in retarding the progress of cancer in different populations of the world.

Key words: Carcinogens, anticarcinogens, Mycotoxins, heterocyclic amines, nitrosamines, polycyclic aromatic hydrocarbons, Resveratrol, Lycopene, Curcumin, Kolaviron.

INTRODUCTION

Among various diseases attributed to mortality in humans all over the world, cancer is a leading cause. Dietary factors continue to play a complex and multifaceted role in the aetiology of cancer. Apart from cigarette smoking and chronic inflammation and infection, nutrition accounts for up to one third of the total cause of cancer (Sugimura, 2002). Cancers most commonly associated with diet include esophageal, stomach, colon, liver and the prostate.

It is well known that most communities feed on substances of plant and animal origin which most of the times contain before processing chemicals, which are toxic. Of particular interest to toxicologists and nutritionists world wide particularly in the underdeveloped nations are the mycotoxins such as aflatoxins, which are metabolites of certain strains of fungi. These fungi occur principally in soil and decayed vegetation but can contaminate food accidentally. In addition, another group of toxins are the fumonisins which are the most important field fungi of maize in Africa and other parts of the world. *Fusarium* species have been shown to produce over 100 secondary metabolites that can adversely affect human

and animal health (Visconti, 2001). Other specific diet-related compounds of concern are the polycyclic aromatic hydrocarbons from roasted and charcoaled grilled meats, N-nitroso compounds that are found in cooked or cured meat and emanating from nitrites. Pyrrolizidine alkaloids in plants, which are used as medicinal herbs, also present a serious risk. These substances have been identified and shown to act as carcinogens in initiating early stages of cancer (Ferguson, 1999).

In light of the considerable complexity of dietary substances, it is not surprising that in addition to mutagenic and carcinogenic components present in the diet, there may exist anticarcinogenic and antimutagenic substances. Thus certain plant-derived and dietary agents have been identified to play a role in the chemoprotection and chemoprevention of diseases caused by dietary carcinogens. This paper examines the present state of knowledge on certain diet-related toxic substances known to cause cancer at some specific sites in the human body and the possibility of preventing these cancers using dietary anticarcinogens.

DIET RELATED CARCINOGENS

Aflatoxins

Aflatoxin B1, the commonest of the aflatoxins is produced by *Aspergillus flavus* (Bradburn et al., 1993). Studies have related exposure of humans to aflatoxin B1 to cancer risk. Although, aflatoxin B1 synergies hepatitis B and C infections in the causation of liver cancer (Turner, 2000), both laboratory and epidemiological data have established the role of aflatoxin in liver carcinogenesis (Groopman et al. 1999). It has been shown that aflatoxin B1 exposure occurs through the consumption of mold-contaminated groundnuts, grains and animal feed (Wogan, 1992), which can be transmitted transplacentally (Denning et al., 1990) and to new borns via breast-feeding (Wild et al., 1987). Aflatoxin contamination has also been linked to male infertility. Recently in a study conducted by Uriah et al. (2001) in Nigerian men, the blood and semen aflatoxin levels ranged from 700 to 1393 ng/ml and 60 to148 ng/ml in infertile and fertile men, respectively. Aflatoxin B1 is known to induce cancer via metabolic activation by CYP3A4, CYP3A5 and/ or CYP1A2 (Ueng et al., 1995; Wang et al., 1998) to *exo*-8,9-epoxide which can form adduct with DNA leading to guanine nucleotide substitutions (Lilleberg et al., 1992) specifically to codon 249 of the *p53* gene (Aguilar et al., 1993). Epidemiological studies have shown increased codon-249 *p53* mutations in areas of high aflatoxin B1 exposure (Greenblatt et al., 1994). Since hepatitis B virus and aflatoxin exposure have also been linked to hepatocellular carcinoma, recent studies have shown the interactive effect of increasing *p53* mutation in persons with hepatitis B and coexposure to aflatoxin (Lunn et al., 1997).

Fumonisins

Fumonisin was discovered in South Africa in 1988 (Marasas, 1995). Fumonisins are a family of toxic and carcinogenic mycotoxins produced by *Fusarium verticillioides* (formerly *Fusarium moniliforme*), a common fungal contaminant of maize (Marasas et al., 2004). Fumonisins have received considerable attention by researchers and have been implicated in the aetiology of a number of diseases such as rat liver cancer and haemorrhage in the brain of rabbits (Marasas, 1995). Fumonisin was reported to induce apoptosis in cultured human cells (Tollenson et al., 1996) and nephrotoxicity in certain animals (Howard et al., 2001).

Although experimental data have not conclusively linked fumonisin contaminated food to human health harzards, but some studies have associated consumption of maize contaminated with fuminisins to human oesophageal carcinoma in some parts of South Africa and China (IPCS, 2000). Recent studies have implicated reactive oxygen species (ROS) in fumonisin toxicity. Stockmann-Juvala et al. (2004) reported increase in lipid peroxidation, production of ROS, increase in caspase-3-like protease activity, internucleosomal DNA fragmentation and intracellular reduction of glutathione in human U-118MG glioblastoma cells treated with fumonisin B1.

Ochratoxins

Ochratoxin A (OTA) is a mycotoxin produced as secondary metabolite by species of *Aspergillus* and *Penicillium* (Van der Merwe et al., 1965). It is found as contaminant in human foods, including various cereals, coffee, cocoa, wines and dried fruits. It is frequently associated with crops grown in semiarid and temperate regions and may not be a major problem in the tropics (Bankole and Adebanjo, 2003). Depending on the dose, OTA may be carcinogenic, genotoxic, immunotoxic or teratogenic (Neal and Judah, 2000). IARC has classified it in group 2B as possibly carcinogenic to humans (IARC, 1993). The kidney has been shown to be a target organ in laboratory rodents and pigs (Kuiper-Godman and Scott, 1989). Exposure to OTA has been associated with the incidence of a kidney disease in humans, involving chronic interstitial nephritis as well as tumours of the urinary tract termed Baslkan Endemic Nephropathy (BEN) because of its geographical distribution (Petkova-Bocharova et al., 1991). It has been reported that co-occurrence of OTA with aflatoxin B1 in the same crop potentiates the mutagenic ability of the latter (Sedmkova et al., 2001).

Studies have shown that the toxicity of OTA does not require metabolic activation in exposed individuals and hence genetic factors may not be involved. Other studies

however, involving specific target nature of some of the OTA-related toxicities and carcinogenesis suggests the involvement of metabolism in these processes (Neal and Judah, 2000). For instance studies using phenobarbitone or 3-methylcholanthrene pretreatment induced 4-hydroxy OTA, a metabolite of OTA by liver microsomes, suggesting the involvement of CYPs1A1/1A2, II B1 and IIA/111 A2 (Omar et al., 1996). On the other hand decreased CYP 450 levels were reported to increase the nepthrotoxicty of OTA, indicating a direct action of the parent compound in the metabolism.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) are compounds formed during incomplete combustion of organic matter (Goldman and Shields, 2003). Many PAH have been established experimentally as carcinogens. Cigarette smoking has also been shown to contribute to PAH burden in man. However, it has been estimated that human diets provide 3 μg PAH/d, which compares to an exposure of 2-5 μg PAH/d per pack of cigarettes in a regular smoker (Goldman and Shields, 2003). Further studies to underscore PAH exposure from diet are the findings that intake of charcoal-broiled meat is more correlated to blood PAH-DNA adducts than smoking (Rothman et al., 1990).

The major carcinogenic compounds among these are benzo(a)pyrene, 1,2,5,6-dibenzanthracene, 3-methylcholanthrene, 7,12-dimethylbenz (a)anthracene and benz (a) anthracene (IARC, 1983). The target organs for PAH are the lung, breast, oropharynx, genitourinary and gastrointestinal tracts (Goldman and Shields, 2003). Our laboratory had screened for the presence of PAH in local foodstuffs available in the Nigeria market. Appreciable amounts of benz(a)anthracene and benzo(a)pyrene were found present in silver cat fish, African mid fish, moon fish, tilapia and smoked meat (suya) purchased from a popular market in Ibadan, Nigeria (Emerole et al., 1982).

Benzo(a)pyrene represents the best characterized PAH compound obtained from the diet. In several animal species, administration of benzo(a)pyrene by different routes has been shown to result in the production of tumors. Thus the administration of a single oral dose of 100 mg benzo(a)pyrene to 50-day- old rats produced mammary tumors in 8 out of 9 animals (Huggins and Yang, 1962). CYP 1A and CYP 1B are group of enzymes known to bring about metabolic activation of PAH to form epoxides. The bay-region diol epoxide binds to DNA as N^2-deoxyguanosine adduct (Cheng et al., 1989). Benzo(a)pyrene adducts have been linked to cancer risk in the lung and they are also associated with site-specific hot spot mutations in the *p53* tumor-suppressor gene (Greenblatt et al., 1994).

In rodents, diets with PAH have been reported to consistently induce cancer of the foregut and lung tumors (Singh et al., 1998). Evidence abounds in humans that dietary exposure to PAH may induce colon cancer (Giovasnnucci et al., 1994). Both animal and human studies indicate that dietary PAH is distributed to other organs besides the locally exposed tissues thus dietary PAH may contribute to other forms of cancer.

N-nitroso compounds

Organic N- nitroso compounds such as nitrosamines, occur either naturally in foods or as the product of *in vivo* reactions between ingested nitrite or nitrogen dioxides and secondary amines (Bababunmi et al., 1978). Nitrosamines have been shown to present serious health harzard. More than 80% of the nitrosamines tested in laboratory animals have been shown to be carcinogenic (Bartsch et al., 1987). Cancer of the liver, lung, kidney, mammary gland, stomach, pancreas, bladder or esophagus has been reported (Lijnsky, 1990). In humans, dietary nitrosamines have been implicated in the etiology of gastric, esophageal, nasopharyngeal and other gastrointestinal cancer (Bartsch et al., 1987).

N-nitrosamines are considered an important carcinogen in parts of China and Japan (Goldman and Shields, 2003). Nitrosamines have been detected in foods and local beverages in certain parts of Nigeria. A survey to determine the extent of the nitrosamine contamination of some popular fermented Nigerian beverages by dimethyl- and diethylnitrosamine was carried out in the Lagos, Ogun, Oyo, Ondo, Kwara and Benue States of Nigeria, following the mass spectrometric detection of these carcinogens in palm wine and nono (sour milk). The results indicated the contamination of drinks, namely, palm-wine, nono, pito, burukutu, and ogogoro, by both nitrosamines at the part per billion level (0.6 - 22 μg nitrosamine/l) (Maduagwu et al., 1979). N-nitroso compounds were also detected in commercially available samples of Nigerian lager beers and bottled palm wine, and of root cuttings of medicinal plants (Maduagwu and Uhegbu, 1986). Nitrosamines have also been shown to be formed by bacteria action. Evidence abounds to show that microorganisms in palm wine are involved in the formation of nitrosamine and that the rate of nitrosamine formation increases linearly with fermentation time (Joaquim, 1973).

Using a combination of chemiluminescence detection on a Thermal Energy Analyzer and gas chromatographic technique, Atawodi and Spiegelhalder (1994) detected certain primary and secondary amines in some tropical plants of medicinal importance in Nigeria. Recently preformed volatile N-nitrosamines namely N-nitrosodimethylamine (NDMA) was detected in the range of 1.2-3.4 μg/kg in four out of the 29 samples of certain Nigerian medicinal plant preparations indicating that microbial contamination of medicinal plant preparations may contribute to N-nitroso compound formation (Atawodi, 2003).

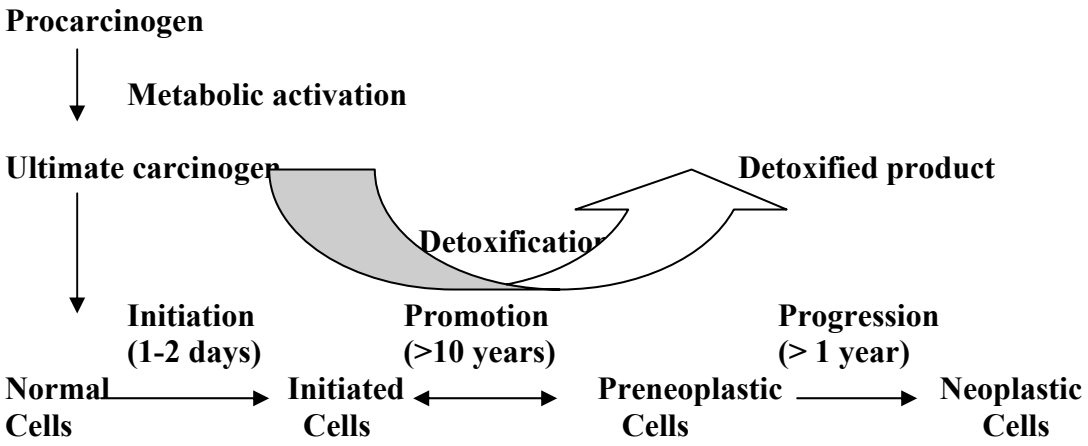


Figure 1. Mechanisms of multistage carcnogenesis.

N-nitrosamines represent a large group of compounds with a general mechanism of cancer induction. For instance, N-nitrosodimethylamine resulting from dietary exposure undergoes enzymatic hydroxylation and subsequent hydrolysis to an aldehyde and a monoalkylnitrosamine that rearranges and releases a carbocation that is reactive toward DNA bases (Loeppky, 1999). CYP2E1 and CYP2A6 have been implicated in the hydroxylation reaction (Kamataki, 1999).

Heterocyclic amines

Heterocyclic amines (HCAs) are formed from pyrolysates or heated materials from amino acids, proteins and meat (Sugimura, 1986). A number of HCAs have been purified and characterized and their carcinogenicity has been demonstrated in rodents. In rats and mice HCAs target the liver, lung, urinary bladder, small and large intestines, forestomach, skin, oral cavity, mammary glands, clitoral gland and prostate in the ventral lobe (Sugimura, 2002).

HCAs have been shown to undergo metabolic activation to exocyclic amino groups and into hydroxyamino groups. CYP 1A2 isoform has been implicated in this conversion (Sugimura, 2002). Further activation may take place due to sulfonation or acetylation to form DNA adducts. The nitrenium ion has been proposed to be the likely ultimate carcinogen binding to the DNA bases (Colvin, 1998). Aside from CYP activation of HCAs, cyclooxygenase catalysed reaction has recently been proposed (Wiess et al., 2001). HCAs have been detected in the urine of volunteers taking ordinary dishes (Knize et al., 1997). Epidemiological studies have revealed the carcinogenicity of HCAs particularly colon cancer (Schiffman and Felton, 1990) but inconsistent results have been produced (Augustsson et al., 1999).

MECHANISM OF CARCINOGENESIS

Experiments in laboratory animals have characterized cancer formation as a series of complex steps. Generally cancer development has been considered to consist three major steps namely initiation, promotion and progression (Figure 1). Initiation, which is an irreversible process, starts when normal cells are exposed to carcinogenic substances and their DNA undergo damage that remain unrepaired or misread. In chemical carcinogenesis, initiation involves the uptake of a given carcinogen, which is subsequently distributed to organs for metabolism. Metabolic activation leads to reactive (electrophilic) species, which can bind to DNA rather than excretory carrier molecules.

The binding can then cause coding errors at the time of replication leading to mutation. The somatic mutation in a damaged cell can then be reproduced during mitosis to produce clones of mutated cells. The next stage in the carcinogenesis process, which is promotion, is the expansion of the damaged cells to form an actively proliferating multi-cellular premalignant tumor cell population. The last stage known as progression is the irreversible process, which produces new clone of tumor cells with increased proliferative capacity, invasiveness and metastasis.

MECHANISMS OF ANTICARCINOGENESIS

Classifications of anticarcinogens

Several classifications of the mechanisms of anticancer agents have been proposed by a number of investigators. Wattenberg (1985) subdivided anticarcinogens into two major categories; blocking agents and suppressing agents on the basis by which they exert protective effect at specific stages of multi-step carcinogenesis. Blocking

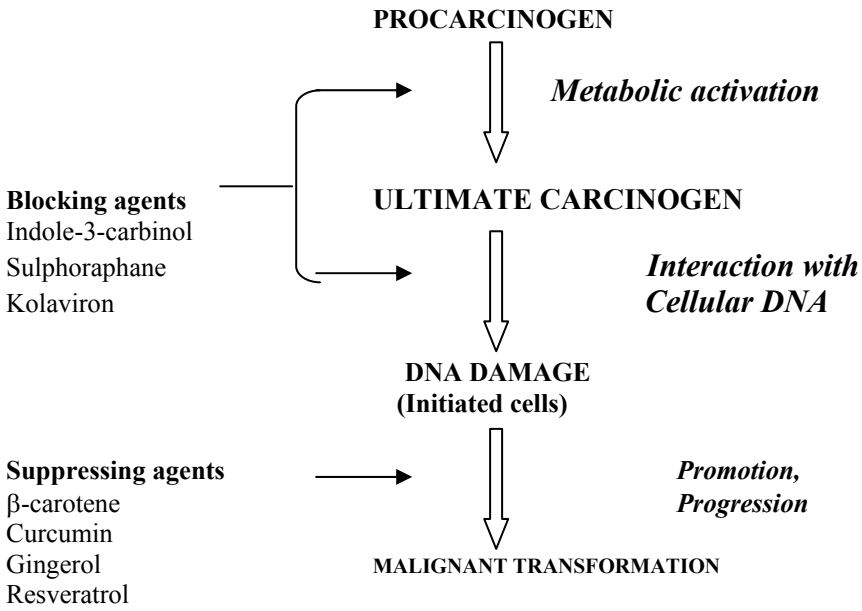


Figure 2. Classification of chemopreventive agents based on their mechanisms of action (Modified from Surh, 1999).

agents are substances that can inhibit initiation either by inhibiting the formation of carcinogens from precursor molecules or reactive intermediates from the parent carcinogens, or by preventing the ultimate electrophilic species from interacting with macromolecules such as DNA, RNA and proteins (Figure 2). Suppressing gents act at the promotion or the progression stage by preventing the malignant expression of initiated cells. Some classifications of anticarcinogens distinguish inhibitors based on their intervention level throughout the process leading from a normal cell to an initiated cell, and then to dysplasia of increasing severity up to carcinoma in situ, and ultimately to cancer (Kelloff et al., 1994).

De Flora (1998) presented a detailed classification of mechanisms of inhibitors of mutagenesis and carcinogenesis. A revised and updated classification was also proposed recently (De Flora et al., 2001). Accordingly, the classification took into consideration the multiple phases involved in the pathogenesis of cancer-related diseases. It analyzed first the inhibition of mutation and of cancer initiation, either extracellularly or inside the cells and then the mechanisms interfering with promotion, progression, invasion and metastasis. A modified scheme incorporating possible points of intervention and some examples of dietary anticarcinogens proposed by De flora (1998) is presented in Table 1.

Cancer chemoprevention

In general terms three different levels of disease prevention has been identified namely primary prevention secondary prevention and tertiary prevention. Primary prevention means preventing the occurrence of diseases. Secondary prevention involves early diagnosis and intervention particularly at the preclinical stage with the objective of reversing, inhibiting or delaying the progress of the disease condition. Tertiary prevention deals with the reduction of the impact of the disease via prevention of complication and early deterioration (Last et al., 1986).

The major part of the classification proposed by De flora (1998) falls within the scope of classification of chemopreventive agents based on their mechanisms of action. The term Chemoprevention, originally coined by Sporn and Roberts who used retinoids to inhibit experimental carcinogenesis (1984), is defined as the use of chemical substances (natural or synthetic) or their mixtures to suppress, delay or reverse the process of carcinogenesis (Surh, 1999). Chemoprevention therefore incorporates primary and secondary prevention while inhibition of invasion and metastasis is conversely outside chemoprevention and falls within tertiary prevention (De Flora, 1998).

Biomolecular mechanisms of enzyme induction

The probability that a carcinogen will reach a target cell and interact with DNA to cause damage is dependent on essentially two complementary mechanisms. Dietary carcinogens such as the aflatoxins, polycyclic aromatic hydrocarbons, heterocyclic amines and nitrosamines require metabolic activation to cause DNA damage and procarcinogens thereby modifying or creating functional groups in the molecule. Anticarcinogens can elicit

Table 1. Mechanisms by which dietary carcinogens protect against cancer.

Mechanisms	Examples
Inhibition of cancer initiation by cellular mechanisms	
Blocking or competition	
Scavenging of reactive oxygen species	Provitamins and vitamins (β- carotene, Vit.C, VitE, polyphenols ,including epigallocatechin gallate and various anthocyanins.
Protection of DNA nucleophiles	Ellagic acid, retinoids, polyamines
Stimulation of trapping and detoxification in non - target cells	N-acetyl cysteine
Modification of transmembrane protein	Short chain fatty acids caproate, caprylate), acylglycosylsterols, dietary calcium
Modulation of xenobiotic metabolizing enzymes	
Inhibition of procarcinogen activation	Isothiocyanates monocyclic monoterpenes (limonene, methol, carveol),retinoids, flavonoids, wheat bran.
Induction of detoxification pathways	Polyphenols, indoles, diterpene esters, riboflavin 5'-phosphate, S-allyl-L- cysteine, allylic sulphides
Inhibition of tumor promotion	
Inhibition of genotoxic effect	Chlorophyllin, retinoids, Oltipraz, natural and synthetic phenols
Induction of cell proliferation	Retinoids, calcium, deltanoids, 5'-azacytidine
Antioxidant and scavenging of free radicals	Provitamins and vitamins(β- carotene, Vit.C, VitE), polyphenols
Inhibition of tumor progression	
Signal transduction modulation	PKC inhibitors (tamoxifen, glycyrrhetinic acid, staurosporine.
Inhibition of proteases	A variety of protease inhibitors
Effects on the immune system	Selenium, lipotropes, retinoids, vaccination with tumor-specific antigens

Classification modified from De Flora (1998).

protection by inhibiting Phase 1 enzymes and/or byinduction of phase 2 enzymes, which leads to detoxification of the carcinogens. Monofunctional inducers induce phase 2 enzymes via the antioxidant/electrophile response element (ARE/EpRE) while bifunctional inducers induce both phase 2 and certain phase 1 enzymes through the Ah receptor and xenobiotic response element (XRE) (Greenwald et al., 1995).

SELECTED EXAMPLES OF DIETARY ANTICARCINOGENIC AGENTS

Resveratrol

Resveratrol, trans-3,5,4'-trihydroxystilbene, is present in various plants, including grapes, berries and peanuts. A phytoalexin, it has been suggested to play pivotal role in cancer chemoprevention on the basis of its potent inhibitory effects on a number of cellular events linked with cancer initiation, promotion and progression (Surh, 1999).

It has been speculated that at low doses (such as consumed in the common diet), resveratrol may have cardioprotective activity. *In vitro* and *in vivo* animal studies indicate that resveratrol modulates vascular cell function, inhibits LDL oxidation, suppresses platelet aggregation and reduces myocardial damage during ischemia-reperfusion (Bradamante et al., 2004). Other mechanism by which resveratrol protects the cardiovascular system include promotion of vasorelaxation, protection and maintenance of intact endothelium, anti-atherosclerotic properties, and estrogen-like actions (Hao and He, 2004). Besides cardioprotective effects, resveratrol exhibits anticancer properties, as suggested by its ability to suppress proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers, multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid; melanoma; head and neck squamous cell carcinoma; ovarian carcinoma; and cervical carcinoma (Aggarwal et al., 2004; German and Walzem, 2000).

In mechanistic terms resveratrol has been reported to be a potent inhibitor of hepatic cytochrome P450-

linkedenzymes involved in the oxidative metabolism of some polycyclic aromatic hydrocarbons (Teel and Huynh, 1998). It is also a potent inducer of phase 2 enzymes such as DT-diaphorase (Uenobe et al., 1997). One other mechanism accounting for the chemopreventive role of resveratrol is its ability to suppress cycloxygenases (COX). Thus resveratrol was shown to inhibit COX-1 activity in microsomes of sheep seminal vesicles (Jang et al., 1997) and inhibition of the inducible isozyme COX-2 in cultured human mammary epithelial cells (Subbaramaiah et al., 1998). Resveratrol has been shown to suppress the activation of several transcription factors, including NF-kappaB, AP-1 and Egr-1 (Aggarwal et al., 2004; Kundu and Surh, 2004).

Lycopene

Lycopene is a carotenoid abundantly present in tomatoes but in smaller amounts in other fruits such as grapefruit, guava, watermelon and papaya (Nguyen and Schwartz, 1999). The significant antioxidant activity of lycopene has been reported. Hsiao et al. (2004) reported the scavenging activity of lycopene on DPPH radical in rat brain homogenates and its ability to inhibit nitric oxide formation in cultured microglia stimulated by lipopolysaccharide. The authors further demonstrated the protective effect of lycopene on ischemic brain injury *in vivo.*

Epidemiological evidence strongly suggests that lycopene consumption and tomato products contribute to prostate cancer risk reduction. Experimental studies indicate that lycopene acts via different mechanisms, which have the potential to cooperate in reducing the proliferation of normal and cancerous prostate epithelial cells, in reducing DNA damage, and in improving oxidative stress defense. The mechanisms include inhibition of prostatic IGF-I signaling, IL-6 expression, and androgen signaling (Wertz et al., 2004). Moreover, lycopene improves gap-junctional communication and induces phase II drug metabolizing enzymes as well as oxidative defense genes. Lycopene was also demonstrated to inhibit mitogen-activated protein kinases, such as ERK1/2, p38 and JNK, and the transcription factor, nuclear factor-kappaB (Kim et al., 2004).

Curcumin

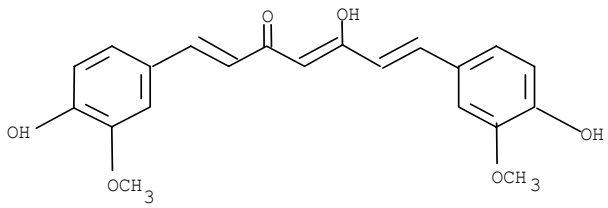
Curcumin (diferuloylmethane) is the natural yellow pigment in turmeric isolated from the rhizome of the plant *Curcuma longa*. It has gained wide acceptance in the Asian countries and it gives specific flavor and yellow colour to curry (Eigner and Scholz, 1999). Curcumin was found to inhibit the generation of ROS including superoxide dismutase and hydrogen peroxide in peritoneal macrophages (Joe and Lokesh, 1994). It inhibits lipopolysaccharide and interferon-γ-induced production of nitric oxide in macrophages (Brouet and Oshima, 1994) and inhibition of inducible nitric oxide synthase gene expression in isolated BALB/c mouse peritoneal macrophages (Chan et al., 1998). Curcumin as an anti-inflammatory agent inhibits the proliferation of several tumour cells (Dorai et al., 2001). It exhibits anti clastogenic (Araujo and Leon, 2001), anti-fungal (Bartine and Tanaoui-Elaraki, 1997) and anti-viral properties (Barthelemy et al., 1998).

Chemopreventive activity of curcumin has been indicated when administered before, during and after carcinogenic treatment as well as when administered during the promotion and progression phase of colon carcinogenesis in rats (Kawamori et al., 1999). Thus it has been shown that curcumin inhibited tumor initiation induced by benzo(a)pyrene and 7, 12-dimethylbenz(a)anthracene and tumor promotion induced by phorbol esters (Deshpande and Maru, 1995; Huang et al., 1995). Curcumin showed a dose-dependent decrease in cytochrome P450 and aryl hydrocarbon hydroxylase activity with a concomitant decrease in B(a)P-DNA adduct in cells treated with benzo(a) pyrene (Deshpande and Maru, 1995) . A similar study also revealed the inhibition of cytochrome P450 1A1 activity and formation of carcinogen-DNA adducts in 7, 12 dimethylbenzanthracene-treated human mammary epithelial carcinoma (MCF-7) cells by competitively binding to the aryl hydrocarbon receptor (Ciolino et al., 1998).

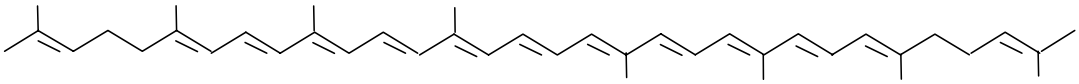
Kolaviron

Kolaviron, a fraction of the deffated ethanol extract, containing *Garcinia* biflavonoid GB-1 GB-2 and kolaflavanone was isolated from the seed of *Garcinia* kola (*Guttiferae*) (1wu, 1985). The chemopreventive role of kolaviron in the presence of several heatocarcinogens (Farombi et al., 2000; Farombi, 2000; Farombi et al., 2001; Farombi 2003a) and renal toxicant (Farombi et al., 2002a) has been well documented. Moreover kolaviron elicited significant hypoglycaemic effects when administered to normal and alloxan diabetic rabbits (Iwu et al., 1990). It also inhibited rat lens aldose reductase activity with an IC50 value of 5.4 X 10^{-6} suggesting the potential use of this compound as an antidiabetic agent. Kolaviron had been reported to interfere with hepatic drug metabolism (Braide, 1991; Farombi 2003b).

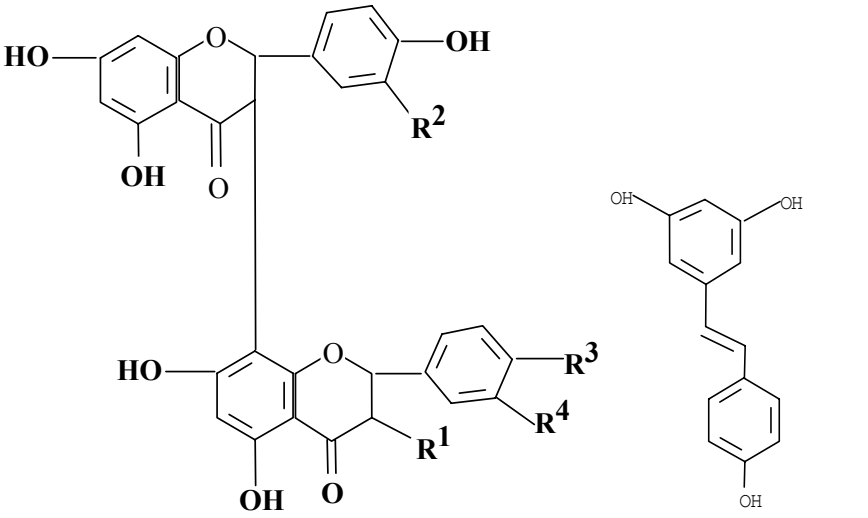
Our data suggest that kolaviron does not affect phase 1 drug metabolizing enzymes as judged by preservation of some representative phase 1 enzymes such as aniline hydroxylase (CYP 2E1), aminopyrine *N*-demethylase (CYP 2B1), ethoxyresorufin *O*-deethylase (CYP 1A1) and *p*-nitroanisole *O*-demethylase (CYP 2C11) (Farombi, 2000). Our results however showed that kolaviron elicited a marked elevation in the activity of two phase 2 representative enzymes- uridyldiphosphoglucuronosyl



Curcumin



Lycopene



Kolaviron **Resveratrol**

	R1	R2	R3	R4
GB1	OH	H	OH	H
GB2	OH	H	OH	OH
Kolaflavanone	OH	H	OMe	OH

Figure 3. Chemical structures of some chemopreventive agents.

transferase (UDPGT) and glutathione *S*-transferase transferase (UDPGT) and glutathione *S*-transferase (GST).

The induction of phase 2 enzymes by kolaviron has been confirmed by the findings of Nwankwo et al. (2000) in Hep G 2 cells. The authors showed that GST isozyme α-1 and α-2.2 were induced by 2.2- and 2.5 fold levels respectively for their messages as determined by reverse transcription polymerase chain reaction (RT-PCR) and northern analysis and 2 fold increase in GSTα protein by western blotting when the cells were treated with CYP3A4 gene transcript by 3.7 fold at a concentration of 90 μmol/l using northern blotting analysis (Nwankwo et al., 2000). Thus kolaviron may be classified as a

bifunctional inducer according to the classification of (Greenwald et al. (1995).

The antioxidant and antiradical properties of kolaviron has been reported. Our data showed that kolaviron (1.5 mg/ml) elicited 85% inhibition of H_2O_2 scavenged superoxide generated by phenazine methosulfate NADH (PMS-NADH). (Farombi et al., 2002b), scavenged hydroxyl radicals by inhibiting the oxidation of deoxyribose and inhibited lipid peroxidation *in vivo* (Farombi et al., 2000, Farombi, 2000). The antioxidant activity of kolaviron was further demonstrated by its ability to reduce background levels of protein oxidation biomarker (2-amino-adipic semialdehyde) in both plasma and liver of rats treated with kolaviron (200 mg/kg body weight) and decreased oxidative damage to DNA in the rat liver (Farombi et al., 2004a). Kolaviron was further demonstrated to significantly inhibit H_2O_2- and GSH/Fe^{3+}-induced strand breaks as well as ENDO III, and FPG sensitive sites, in human lymphocytes as well as rat liver cells (Farombi et al., 2004b).

CONCLUDING REMARKS

Humans are unavoidably exposed to carcinogenic agents such as the heterocyclic amines, mycotoxins and other dietary carcinogens such as the nitrosamines. Although each one of these examples only occurs at low levels but the presence of these genotoxic substances may result in synergistic effects leading to cancer in humans. Chemopreventive strategies designed to limit both exposure to and the adverse health effects from dietary carcinogens are important public health goals to attenuate the incidence of diet-related neoplastic diseases since the complete elimination of exposure to these agents is not possible. It is reassuring that many food constituents consumed by the population contain potentially cancer preventive agents which are effective in preclinical models owing to their intrinsic antioxidant and anti-inflammatory properties. In view of the multifacet action of these naturally occurring chemopreventive agents, clinical application should be considered. However, one of the aspects that pose serious challenge to the future is to find, validate and introduce appropriate biomarkers for evaluating the results of cancer chemopreventive treatments.

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