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Natural Antimutagens: A Review

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ABSTRACT

Mutagens are not only involved in genotoxicity and carcinogenesis but also involved in the inception and pathogenesis of several chronic degenerative diseases including hepatic disorders, neurodegenerative disorders, cardiovascular disorders, diabetes, arthritis, chronic inflammation and in the process of ageing. One of the best ways to minimize the detrimental effects of mutagens is by the use of natural antimutagens. Naturally occurring antimutagenic principles present in plants, human diet and other sources have protective effects against mutagens. These include flavonoids, phenolics, coumarins, carotenoids, anthraquinones, tannins, saponins and many more. Present review attempts to furnish a brief overview on natural products conferring antimutagenicity.

Key words: Mutation, mutagenesis, antimutagenic, *S. typhimurium*

INTRODUCTION

Mutations are the cause of innate metabolic defects in cellular systems, triggering morbidity and mortality in living organisms. A plethora of synthetic and natural substances, apart from various genotoxic physical and biological agents are known to act as mutagenic, co-carcinogenic and/or carcinogenic agents. There is increasing evidence that mutation in somatic cells are not only involved in the carcinogenesis but can also cause genetic disorders like atherosclerosis, heart diseases and several other degenerative disorders (DeFlora *et al*., 1996). Since, the mutagens are involved in the initiation and promotion of several human diseases, including cancer, the significance of novel bioactive phytocompounds in counteracting these pro-mutagenic and carcinogenic effects is now gaining credence. Such chemicals that reduce the mutagenicity of physical and chemical mutagens are referred to as antimutagens (Mitscher *et al*., 1986).

Numerous studies have been carried out in last four decades in order to identify compounds that might protect humans against DNA damage and its consequences. There are continued efforts all over the world to explore the rich biodiversity of edible as well as medicinal plants and other edible non-toxic plants in pursuit of the most effective phytoantimutagens. These bioactive compounds belong to a variety of different chemical groups such as phenolics, pigments, allylsulfides, glucosinolates, tannins, anthocyans, flavonoids, phytosterols, protease inhibitors and phytoestrogens. Many of these substances elicit, apart from their antimutagenic and anticarcinogenic properties, additional beneficial effects such as activation of the immune system and/or protection against cardiovascular diseases (Middleton and Kandaswami, 1993).

The group of chemicals that cause cancer in man and animals are collectively referred to as carcinogens. Environmental pollution is associated with increased risk of cancer. Prevention of cancer and other mutation related diseases can be pursued by avoiding exposure to recognized carcinogens or mutagens, by favoring the intake of protective factors and by fortifying physiological

defense mechanism. Moreover, there is an increasing awareness that certain naturally occurring substances in plants and other source have protective effects against environmental mutagens or carcinogens and also endogenous mutagens. Hence, research work related to the discovery, characterization and use of antimutagenic agents is receiving considerable attention. A large number of experimental reports have begun to appear in the scientific literature, wherein increasingly more natural antimutagens have been identified, isolated and found to possess significant mutation chemoprevention properties. In this review promise of these natural antimutagens has been focused upon.

MUTATION, MUTAGENS AND ANTIMUTAGENS

Mutation: Mutation refers to heritable change in nucleotide sequence or number occurring due to alteration in the sequence of the code in a gene due to change, removal or insertion of one or more bases in a gene resulting in an altered gene product (Hartl *et al*., 1994). This change may be expressed, for example as change in the structure of a protein which alters or abolishes its enzymatic properties. Mutation occurs spontaneously or may be induced by several physical, chemical or biological agents. In general, mutations are detrimental because in most cases they lead to defects in cellular functions. Mutations cause permanent alteration in DNA structure, which have been implicated in the etiopathology of cancer and other degenerative diseases. The chemical and physical factors that induce mutation are called mutagens and those that reduce their mutagenicity are called antimutagens (Venitt and Parry, 1984).

Mutagens: The substances which can induce mutations are known as mutagens. These include, physical agents like Ultra Violet (UV) and X-rays which cause the deletion of nucleotide. These agents produce a variety of lesions in DNA including strand break, base damage and dimerisation of bases. Many diverse environmental, industrial, dietary and natural chemicals are capable of inducing mutation and genotoxic effects. There is evidence that mutation in somatic cells causes cancer, genetic disorders and many other degenerative disorders including arthritis and connective tissue disorders, hepatic disorders, neurodegenerative disorders, cardiovascular disorders, diabetes, chronic inflammation, ageing etc. The mutagenic effects of genotoxic chemicals are additive, cumulative and sometimes irreversible (Hartl *et al*., 1994).

Antimutagens: An antimutagen can prevent the transformation of a mutagenic compound into mutagen, inactivate the mutagen or otherwise prevent the reaction between mutagen and DNA. Another kind of antimutagens may induce, repress or inactivate directly or indirectly the enzymes of the DNA repair recombination and replication pathways. The antimutagens can be classified as: desmutagens and bio-antimutagens (Ferguson, 1994).

Desmutagens: These are substances, which inactivate the mutagens partially or fully by enzymatic or chemical interaction before the mutagen attacks the genes. These must be considered only as apparent antimutagens.

Bio-antimutagens: These are regarded as true antimutagens. They suppress the process of mutation after genes are damaged by mutagens. They act on the repair and replication processes of the mutagen damaged DNA resulting in a decline in mutation frequency.

MECHANISM OF ANTIMUTAGENESIS

The major mechanisms of antimutagenesis can be broadly described as under (DeFlora *et al.*, 1992):

- Chemical or enzymatic inactivation
- Prevention of formation of active species
- Scavenging
- Antioxidant free radical scavenging

Chemical or enzymatic inactivation: Many mutagens, which are reactive, acting not only on DNA but also on proteins and enzymes can be directly inactivated by a range of different chemicals. Antimutagenic and anticarcinogenic properties have been associated with both inhibitors and inducers of cytochrome P-450 enzymes such as indole-3-carbinol. Inducers of phase-II metabolic enzymes such as glutathione transferase tend to inhabit a wide range of target carcinogens e.g., isothiocyanates such as benzyl isothiocyanate and antioxidants such as 2, 3-*tert* butyl-4-hydroxy-anisole (BHA).

Prevention of formation of active species: Many genotoxic mutagens or carcinogens require metabolic activation or bio-activation to an electrophilic from (the active species) that can react with the DNA. Although these processes commonly occur in the liver, there is increasing evidence for metabolic activation by other tissues also, especially for the GIT. N-nitro compounds are often formed in the stomach through a reaction form nitrite and secondary or tertiary amines.

Scavenging: A number of desmutagens are able to scavenge dietary mutagens through binding or adsorption . In general the mutagen remains intact during this process but is unable to react with DNA. Chlorophyllin and some dietary fibers appear to act in this way.

Antioxidant and free radical scavenging: Free radicals can damage DNA and cause mutagenicity and cytotoxicity and thus play a key role in carcinogenesis. It is believed that Reactive Oxygen Species (ROS) can induce mutations and inhibit DNA repair process, that result in the inactivation of certain tumor suppressor genes, leading to cancer. A wide range of antimutagenic agents have antioxidant or free radical scavenging activity e.g., carotenoids, flavonoids and phenolic compounds. These agents can readily scavenge most free radicals especially those having a short half life e.g., OH radical.

JANUS CARCINOGENS AND MUTAGENS

Many substances reported to be antimutagens have themselves been shown to be promutagenic or carcinogenic. Chemicals belonging to such a category are termed Janus carcinogens and mutagens after the ancient Roman God Janus who had been depicted as having one head with two faces, one looking forward and one looking backward. Several other recent reports have also addressed or emphasized the biphasic nature of many active substance reported to modulate the mutagenicity or carcinogenicity of heterocyclic amines. The majority of these modulating substances are plant products or extracts. Extensive study of the antimutagenicity literature by Waters *et al.* (1996) showed that a number of chemicals have both antimutagenic mutagenic effects. For instance, β-carotene was the first presumptive anticarcinogen to be included in large-scale, clinical

intervention trials, but the trials were terminated prematurely upon revelation that β-carotene treatment was associated with an increased cancer incidence rather than the expected decrease. Other examples include, testosterone, β-oestradiol, diethylstilbesterol, vanillin etc.

NATURAL ANTIMUTAGENIC AGENTS

Extensive research in the last few decades on the detection and characterization of antimutagenic compounds from edible, non-edible and medicinal plants and marine organisms has demonstrated a great diversity. Several authors have suggested that natural antimutagens may belong to any of the following major class of compounds. Major emphasis has been laid on the flavonoids, phenolics, carotenoids, coumarins, anthraquinones, tannins, terpenoids, saponins and several others all of which are secondary plant metabolites. More than 500 compounds belonging to at least 25 chemical classes have been recognized as possessing antimutagenic/protective effects (Boone *et al*., 1990). In recent years, there has been an increased interest in identifying the antimutagenic and anticarcinogenic constituents of both dietary and medicinal plants all over the world. The major classes of antimutagenic compounds are briefly described below.

Vitamins: Vitamins have been extensively studied for their antimutagenic potential. Vitamin C and E have been shown to be antimutagenic against doxorubicin induced chromosomal aberrations (Antunes and Takahashi, 1998). Vitamin A, C and E were found to be antimutagenic towards Methyl Azoxy Methanol (MAM) induced mutagenesis in *Salmonella typhimurium* strain TA100 (Tavan *et al*., 1997). Vitamin C (ascorbic acid) when administered concurrently with a pesticide showed significant decrease in the frequency of pesticide induced mutations (Kuroda, 1990).

Flavonoids: Flavonoids are a class of phytochemicals that possess antimutagenic properties in addition to a wide range of biological activities. Flavonoids present an important class of antimutagens and anticarcinogens with high potential. Distinct structure activity relationship were detected when 56 flavonoids, 32 coumarins, 5 naphthoquinones and 12 anthraquinones were tested for their antimutagenic potencies, with respect to mutagenesis induced by 2-nitrofluoro 3-nitro fluoranthene and 1-nitropyrene in *S. typhimurium* TA98. Among flavonoids, all flavones and many flavonoids with phenolic hydroxyl group like leuteolin, kaempherol etc., exerted antimutagenicity chalcones and dihydrochaleones were potent antimutagens (Edenharder and Tang, 1997).

A number of known flavonoids including flavonoid glycosides and isoflavones were reported to possess significant antimutagenic activity. Citrus juice flavonoids are reported to possess anticarcinogenic and antimutagenic properties (Calomme *et al*., 1996). Heo *et al*. (1992) tested 14 flavonoids including flavones and flavonol derivatives for their antimutagenic effect against induction of micronuclei by benzo[α]pyrene (Bap) in polychromatic erythrocytes (PCEs) of mice.

Isolation of two new isoflavones, fremontin and fremontone from the root of *Psorothamnus fremontii* was reported, which are highly active in the inhibition of mutagenicity of Ethyl Methane Sulfonate (EMS) at all concentrations tested (Manikumar *et al*., 1989). Antimutagenic effect of hispidulin and hortensin, the flavonoids from *Millingtonia hortensis* was seen when tested against 2-amino anthracene, aflatoxin B_1 induced mutation (Chulasiri *et al*., 1992). Other flavonoids include glaberene from *Glycyrrhiza glabra*, quercetin, myricetin, kaemferol, hesperidin and other flavonoids isolated from *Ocimum javonica*. Antimutagenic activity all these flavonoids has been tested using *S. typhimuricem* against various types of mutagens (Shankel *et al*., 2000).

Phenolic compounds: Phenolic compounds are a widely studied group of compounds from natural food and medicinal plants and are also implicated in various biological activities. Certain phenolic compounds such as ellagic acid found in strawberries, raspberries, grapes, walnuts, etc. have been found to be antimutagenic (Loarca-Pina *et al*., 1996). Also, the compounds such as epicatechin, (-)-epicatechin gallate, (-)-epigallocatechins, (-)-epigallocatechin gallate have been reported to be responsible for the antimutagenic activity of green tea and black tea (Hour *et al*., 1999; Weisburger *et al*., 1996). Ohe *et al*. (2001) studied the antigenotoxic properties of tea leaf extracts in a *Salmonella* umu-test. Geetha *et al*. (2004) demonstrated the antimutagenic activity of green tea catechins against oxidative mutagens such as tertiary butyl hydroxide, hydrogen peroxide using *Salmonella typhimurium* 102 tester strains. Antimutagenic effect of green tea against smoke-induced mutations in humans were investigated by Lee *et al*. (1997) and it was found that green tea can block the cigarette smoking-induced increase in sister chromatid exchange frequency.

Phenolics present in turmeric and clove, namely curcumin and eugenol respectively were found to inhibit the mutagenicity produced by direct acting mutagens such as N-methyl-N'-nitro-N-nitrosoguanidine using *S. typhimuricem* strains TA100 and TA1535 and eugenol inhibited tobacco-induced mutagenesis in Ames test (Soudamini *et al*., 1995).

Anthraquinones: The antimutagenic activity of anthraquinones (aloe-emodin-anthraquinone isolated from *Aloe barborescence*), were reported (Shankel *et al*., 2000). Among compounds structurally related to anthraquinones, anthrone, acridone and xanthone exerted antimutagenecity, anthrone being the most patent one. All naphthaquinones were potent antimutagens, plumbagin and 2-methyl-5-hydroxy naphthoquinone showed exceptional antimutagenicity (Edenharder and Tang, 1997).

Carotenoids: Several studies on carotenoids have shown that they affect activation of promutagens. The water insoluble residues of some carotenoid rich fruits and vegetables such as apricots, arranges, brussels, sprouts, carrots, yellow-red peppers and tomatoes when sequentially extracted with several solvents and tested for inhibition of mutagenicities induced by aflatoxin B_1, benzo[α]pyrene (BaP), imidazoquinoline and cyclophosphamide (CP) in histidine deficient strains of *S. typhimurium*, number of BaP or CP-induced micronuclear in PCEs in bone-marrow of mice was reduced significantly by the carotenoids viz., lycopene, canthxanthin, lutein and β-cryptoxanthin (Rauscher *et al*., 1998).

Antimutagenicity of carotenoids extracted from five different types of green peppers (*Capsicum* sp.) has been reported on *S. typhimurium* tester strain YG1024, against the mutagenicity of some nitroarenes (Gonzalez *et al*., 1998). Antimutagenic activity of β-carotenre, canthaxanthin, β-carotene-8-apo-β-carotenal and 8-apo-β-carotene methyl ester showed a dose dependent decrease in the mutagenicity compared with 1-methyl-3-nitro-1-nitrosoguanidine and benzo[α]pyrene in *S. typhimuium* tester strain (Salvadori *et al*., 1994).

Diterpenoids: Diterpenoid like erythroxydiol isolated from *Aquillaria agallocha* demonstrated antimutagenic as well as antitumor activity (Connolly *et al*., 1965). Four novel dibenzoate diterpenes, pulcherrimins A, B, C and D obtained from roots of *Caesalpinia pulcherrima*, were found to be active in DNA repair-deficient yeast mutant (Patil *et al*., 1997).

Coumarins: Coumarins are chemically 2H-1-benzopyran-2-ones, widely distributed in the plant kingdom. A wide range of structures with varying complexity occurs in angiosperms. Coumarins have been shown to behave both as antimutagenic as well as anticarcinogen. For instance, coumarin, umbelliferone, 8-methoxypsoralen isolated from different plant sources have been found to be antimutagenic (Shankel *et al*., 2000). Psoralen from *Psoralea corylifolia* and imperatorin and osthol from *Selinum monniere* have been described to inhibit mutagenicity induced by benzo[α]pyrene. Wall *et al*. (1988) observed non-toxicity and high activity of several coumarins including psoralen from *Selinum monniere* in the inhibition of mutagenicity of benzo[α]pyrene.

Tannins: Several tannins have been found to reduce the mutagenic activity of a number of mutagens. Their anticarcinogenic and antimutagenic potential has been related to their antioxidative property, which is important in protecting cellular oxidative damage including lipid peroxidation (Chung *et al*., 1998). The anticarcinogenic effect of tannic acid was studied *in vivo* using micronucleus test and it was found that the frequency of micronuclei induced by mitomycin C, ethyl nitrosourea or 4-nitroquinoline-1-oxide in mouse bone marrow cell was decreased by the oral administration of tannic acid 6 h before the mutagen injection, they also observed the antimutagenic effect of tannic acid *in vivo* in the mouse spot test using male PW and female C57BL/10 mice (Sasaki *et al*., 1990). Antimutagenic effects of (+) catechin, ellagic acid and gallic acid against mutagenicity induced by known mutagens were also reported (Toering *et al*., 1996).

Hormonal steroids: Some hormonal steroids have been reported to provide protection against mutagenic effects. Among the steroid molecules bile acids were shown to have antimutagenic activity towards various direct and indirect acting mutagens in the Ames test. Ethinyl oestradiol and mestranol both of which are synthetic derivatives of β-oestradiol largely used in contraceptive pills these were also strong inhibitors of the mutagenicity acting at nanomolar concentrations (Wilpart *et al*., 1986). In experiments using yeast without an external metabolic activation system the hormones testosterone, β-oestradiol and dicthyl stilbesterol were antimutagenic and co-recombinogenic (Fahrig, 1996).

Saponins: As many as thirteen saponins have been isalated from and identified in *Calendula officinalis, C. arvensis, Hedera helix*. Four from *C. arvensis* and three from *H. helix* showed antimutagenic activity against benzo[α]pyrene and a mutagenic concentrate from a smoker with a dose response relationship in modified liquid incubation technique of the Salmonella assay (Elias *et al*., 1990). Ginseng saponin metabolites introduced by human intestinal bacteria were found antigenotoxic against benzo[α]pyrene induced clastogenecity (Lee *et al*., 1998).

Marine products: Certain secondary metabolites found in marine organisms have the capability for inhibiting the mutagenicity towards *S. typhimurium* of a number of mutagens. Elatol and obtusol are the antimutagenic compounds isolated from extract of marine animals known as sea hare. These are halogenated compounds containing bromine and chlorine (Shankel *et al*., 2000). Several halogenated active compounds were also found in red and brown algae. Cymobarbatol and 4-isocymobarbatol were isolated from *Cymopolia barbata*, a green algae guided by antimutagenicity assay (Wall *et al*., 1989).

Miscellaneous compounds: Ajoene and one of the derivatives of allicin are the organosulphur compounds found in garlic extract with significant antimutagenic activity (Ishikawa *et al*., 1996). Alkaloids and triterpenpoids were also reported to possess protective actions (Haldar *et al*., 2010a). Various other miscellaneous groups of phytocompounds, such as caffeine, trigonelline and piperine, have been demonstrated to possess antimutagenic properties (Waters *et al*., 1996). Xanthones such as euxanthone and 1,5-dihydroxy-8-methoxyxanthone isolated from *Visma amazonica* display considerable antimutagenic activity against 2-aminoanthracene and EMS (Monache *et al*., 1983). Haldar *et al*. (2010b) reported preventive effects of *Indigofera aspalathoides* extract against 20-methylcholanthrene-induced carcinogenesis in Swiss mice.

An 80% ethanol extract of lemon grass (*Cymbopogon citrates*) was found to be antimutagenic to various known mutagens in Salmonella mutation assay (Vinitketumnuen *et al*., 1994). This extract was shown to inhibit on the formation of azoxymethane induced DNA adducts and aberrant crypt foci in the rat colon (Suaeyun *et al*., 1997). Essential oil from lemon grass (*Cymbopogon citrates*) that is used as a constituent of Lemongrass Tea in central and Southern parts of India was found to possess antimutagenic activity against lead nitrate and cyclophosphamide induced micronuclei and chromosomal aberration *in vivo* in Swiss albino mice (unpublished observation by the author and co-workers). Its chief constituent citral, a monoterpenoid was reported to possess anticlastogenic activity (Rabbani *et al*., 2005).

Numerous references of antimutagenic activities of various plants and their constituents are found in the literature and newer reports of pharmacological screening continually appear in the scientific literature.

FOOD PRODUCTS AS ANTIMUTAGENS

Dietary components exhibit a wide range of activities that can affect mutagenesis. Naturally occurring substances in foods have been shown in laboratory experiments to serve as dietary antimutagens. Dietary desmutagens may also act later in the carcinogenesis process as tumor growth suppressors. Extensive works were carried out demonstrating the antimutagenic and anticarcinogenic potential of some commonly consumed spices and vegetables such as turmeric, mustard, green leafy and allium species of vegetables (Ferguson, 1994). A human intervention study with vegetable products containing different carotenoids showed that the supplementation of diet with tomato, carrot or spinach products resulted in significant decrease in lyphocyte DNA damage (DeMarini, 1998).

The antimutagenic properties of two dietary supplements garlic and mustard oil were observed against the clastogenic activity of sodium arsenite (Choudhury *et al*., 1997). Garlic extract was found to inhibit the mutagenicity produced by direct acting mutagens such as N-methyl-N'-nitro-N-nitrosoguanidine and sodium azide using *S. typhimuium* strains TA100 and TA1535. This antimutagenic effect of garlic has been attributed to its organosulphur constituents as stated above (Ishikawa *et al*., 1996). Casein showed a strong antimutagenic activity *in vivo* and *ex vivo* in the DNA repair host mediated assay and liquid suspension assay, respectively (Van Boekel *et al*., 1997). Yogurt (a fermented milk product) was reported to be antimutagenic (Bakalinsky *et al*., 1996). Antimutagenic effects of guava (*Psidium guajava*) was reported by Grover and Bala (1993). The mechanism of antimutagenic effects of mushrooms was found to be by direct chemical interaction with the mutagens viz. aflatoxin B_1, benzo[α]pyrene and acridine or inhibition of the activation process in the case of promutagens (Gruter *et al*., 1990). Asafoetida and turmeric extracts were found to inhibit microsomal activation dependent mutagenicity of 2-acetamido fluorine; similar

results were also obtained using Indian spinach leaf extract, curcumin and eugenol which are phenolics present in turmeric and clove, respectively (Soudamini *et al*., 1995). Alkyl-resorcinols, amphiphillic compounds commonly found in cereal grains demonstrated antimutagenicity in Ames test (Jain *et al*., 1987).

OTHER HEALTH BENEFITS BY NATURAL ANTIMUTAGENS

Most of the natural antimutagens exert, apart from their antimutagenic and anticarcinogenic properties, additional health beneficial effects such as immunomodulator, hepatoprotective, antihyperglycemic, antihyperlipidemic, cardioprotective, anti-inflammatory and antirheumatic actions owing to their excellent antioxidant and detoxifying properties (Shankel *et al*., 2000). Some other encouraging observations have been made by some workers during their studies on natural antimutagens. The effects of known antimutagens, namely polyamines and related compounds were studied on the development of drug resistance in a variety of strains and it was found that polyamines produce strong antimutagenic effects against EMS and MMS-induced antibiotic resistance (Pillai and Shankal, 1998). It was proposed that natural antimutagenic agents may prolong the efficacy of human immunodeficiency (HIV) virus therapy which is otherwise affected by the tendency of transfected human immunodeficiency virus therapy to mutate to drug resistant forms. Hence, safe intakes of fruits, green tea polyphenols and cruciferous vegetable were expected to prolong the efficacy of drug therapy in subjects infected with the human immunodeficiency virus (McCarty, 1997).

CONCLUSIONS

Untoward mutations are associated with a number of serious diseases for which useful medication are few and treatment is often limited to deal with symptomatologies, many of the environmental pollutants, residues of pesticides and toxins present in food and drugs are common agents of mutagenic damage in human population. Hence there is a need to find natural antimutagenic agents having the potential to prevent or at least delay the onset and severity of genetic damage, which can be incorporated into the regular diet of an individual. Potentially antimutagenic plants include a number of common or ethnic group restricted edible plants, including cereals, pulses, vegetables and spices and medicinal herbs and health tonic plants. Consumption of dietary green leafy vegetable, fruits, carrots, nuts, beverages and green tea etc. can impart necessary protection against the genotoxic effects of mutagens present in food, drugs, cosmetics, industrial waste etc. and thereby help in prevention of cancer and other degenerative disease like atherosclerosis, diabetes mellitus, ischaemic heart disease, rheumatoid arthritis, neurological disorders etc. The search for non-toxic and broad-spectrum natural antimutagens should be extended through systematic screening of the unexplored rich diversity of plant kingdom.

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