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Chapter

Current Trends and Future Perspectives of Antimutagenic Agents

Adel M. AbdelHakem and El-Shimaa M.N. Abdelhafez

Abstract

Mutation is the process leading to heritable changes in DNA caused mainly by internal and external factors. Recently, studies on mutagenic agents have been increased due to increasing in mutation-related disease. The antimutagenic effect is desired to prevent mutation on genes or to inactivate the mutagenic agent. It seems that the interest in antimutagenic substances displaying multiple mechanisms of action will be an important trend in the research and development of new antimutagenic compounds in the near future. Therefore, this chapter displays various possible mechanisms of action for antimutagenic agent and introduces different types of antimutagens, natural and synthetic, that are considered very important.

Keywords: mutagenesis, antimutagenic, mechanism, natural, synthetic, DNA

1. Introduction

Mutagenicity is the process of induction of permanent heritable changes in the DNA sequence of living systems [1]. It is caused mainly by the external factors, including chemical and physical agents, or can also occur spontaneously due to errors in DNA repair, replicationand recombination [2]. A number of mutagens have been recognized in our environment recently as many factors which modulate the toxic activities either in vitro or in vivo [3]. Agents contributing to mutagenesis in the environment could be from wide-spectrum applications of biocides in the agriculture, industrial sources, and other contaminants [3].

These mutagenic chemicals have severe drawbacks in humans such as cancer and various inherited diseases; therefore, it is important to detect such mutagenic agents precisely and rapidly and also look for solutions to combat them [2].

Natural occurring dietary antimutagens such as healthy protective foods such as fruits and vegetables could strongly counteract the deleterious effect of these mutagens [4]. Additionally, the World Health Organization (WHO) revealed that one-third of all cancer death incidences are preventable depending on the diet type especially health protective phytochemicals that provide an effective solution to these concerns [4]. The current chapter will present the mutagenic events and a brief compilation of the existing scientific findings either from dietary sources or synthetic agents that have the potential activity to combat the disorders caused by

the mutagenic agents, putting in mind possible future perspectives and mechanism of antimutagenics [2].

2. Mechanisms of action

Several classes of antimutagenic compounds may be distinguished based on their mechanism of action as the following:

2.1 Antimutagens with antioxidant potency

Reactive oxygen species (ROS) are generated by many mutagens; therefore, the removal of reactive molecules is considered an important strategy in the process of antimutagenesis. It is reported that compounds with antioxidant propertiescan remove ROS before these molecules react with DNA, resulting in a mutation [5].

It was reported that the antigenotoxic effects of Lipoic acid (LA) (**Figure 1**) against mitomycin-C induced chromosomal aberrations, sister chromatid exchanges, and micronucleus formation was observed in human peripheral lymphocytes. Moreover, LA exhibits both anticlastogenic and antimutagenic activity [6].

2.2 Interaction with mutagen

A potential protective mechanism against mutagenesis is related to the direct chemical interaction between a mutagen and an antimutagenic compound before it induces DNA damage leading to the inhibition of their damaging activity. Sulfhydryl compounds, such as cysteine, can inactivate 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) (**Figure 2**) [7].

2.3 Antimutagen as blocking agents

The mechanism of action for this type of antimutagenics is to prevent mutagenic compounds from reaching target sites such as nucleophilic bichalcophenes (**Figure 3**). They might be able to bind to DNA and, therefore, protect genetic materials from electrophilic mutagenic agents [8].

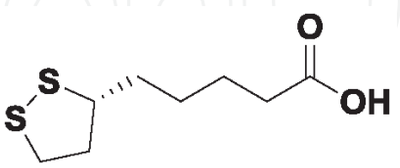


Figure 1.
Lipolic acid.

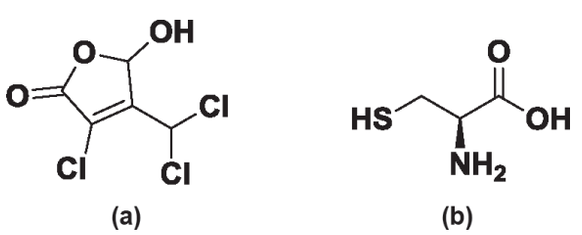


Figure 2.
(a) Mutagen (MX) and (b) antimutagen (cysteine).

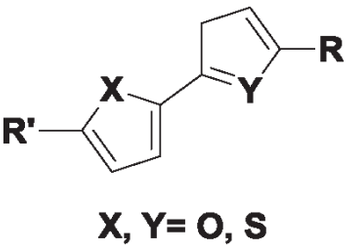


Figure 3.
Bichalcophene derivatives.

2.4 Multifunctionally acting antimutagens

Various antimutagenic agents work through multiple mechanisms affording protection against several mutagens. Noteworthy, the ability of compounds to affect mutagens simultaneously in varied ways significantly enhances antimutagenic effectiveness. Hence, searching for such multifunctionally acting antimutagens is of great importance [9].

2.5 Desmutagenesis

This way of preventing induced cellular mutagenesis depends on mutagens that are inactivated before they can attack the DNA in vitro [3].

2.6 Bio-antimutagenesis

Damaged DNAusually requires fixation steps (e.g., DNAreplication and/or repair) before it can be expressed as stable and heritable mutant genes. Hence this mechanism relates to interference with some aspects of cellular DNA fixation processes working on reducing genetic damage in DNA [3].

3. Antimutagenic agents

Antimutagenic agents are able to combat the disorders caused by mutagens [10]. This group of agents includes both natural and synthetic compounds categories [1].

3.1 Natural antimutagenic agents

The antimutagenic effect of natural sources was investigated due to certain compounds in them or due to whole extract.

3.1.1 Isolated compounds

3.1.1.1 Cinnamaldehyde

It is the first naturally occurring organic antimutagen [11]; it has been involved in screening and chemical studies of such biologically active substances [12]. Antimutagenic action is attributed to either by a selective killing effect of cells which have premutation lesion of DNA via inhibition of the errorprone SOS repair system, or by enhancement of the error-free DNA repair system (**Figure 4**) [13].

3.1.1.2 Punicalagin (PC) and ellagic acid (EA)

Punicalagin is an ellagitannin found in the fruit peel of *Punica granatum*. PC and EA (**Figure 5a, b**) had antioxidant and antigenotoxic properties which dose-dependently and markedly antagonized the effect of tested mutagens such as NaN_3, benzo[a]pyrene, 2-aminoflourine, and methyl methanesulfonate (EMS), with 90% mutagenicity inhibition [14].

3.1.1.3 Luteolin derivatives

Luteolin derivatives (luteolin 7-O-rutinoside, luteolin 7-O-glucoside, and luteolin 7-O-glucuronide) (**Figure 6**) are isolated from *Mentha longifolia* (L.) to evaluate the antimutagenic activities by using Ames *Salmonella* test (TA 1535 and TA1537 strains). The antimutagenic activity on TA1537 was 87.63, 84.03, and 67.77%, respectively. The antimutagenic activity of these compoundscan be due to

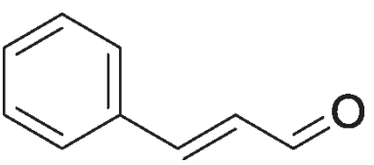


Figure 4.
Cinnamaldehyde.

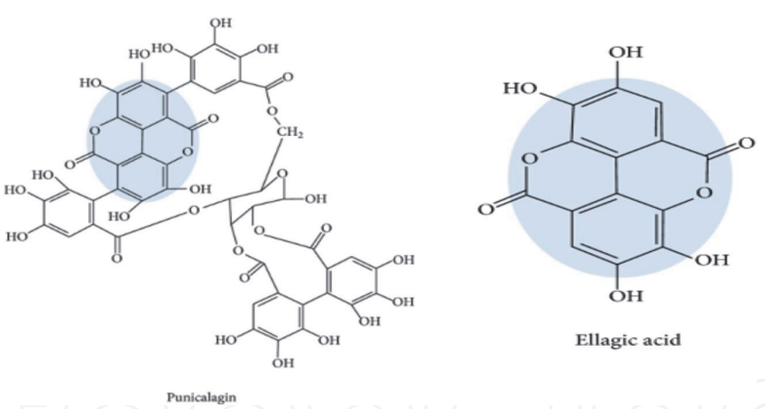


Figure 5.
(a) Punicalagin (b) ellagic acid.

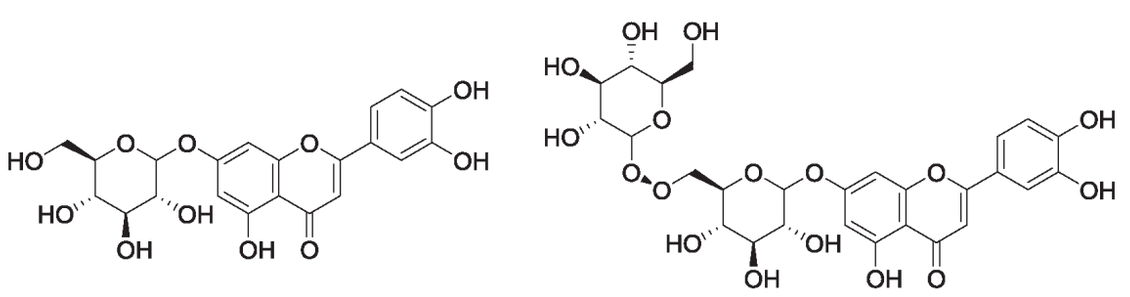


Figure 6.
Luteolin derivatives.

the inhibition capability by blocking 9-aminoacridine binding to DNA [15]. In addition, the inhibition effects against ethyl methanesulfonate may be related to the protection against DNA double-strand breaks or EMS alkylating action (**Figure 6**) [16].

3.1.1.4 Acetogenins

Annona crassiflora Mart. (AcM) is a Brazilian plant, *araticum*, which is widely used as a therapeutic medicine to treat several diseases such as rheumatism, diarrhea, and syphilis. Ethanolic extract were evaluated for antimutagenic and cytotoxic effects. The results indicated an antimutagenic activity of the AcM due to the presence of acetogenins (**Figure 7**) and other flavonoids [17].

3.1.1.5 Pinocembrin and cardamonin

Pinocembrin and cardamonin (**Figure 8**) are found in Sozuku (Chinese drug from dried seed of *Alpinia katsumadae* HAYATA). These compounds showed potent antimutagenic activity against 2-amino3,4-dimethylimidazo-[4,5-f] quinolone (MeIQ) mutagenesis in Ames test using the *S. typhimurium* TA100 and TA98 strains [18].

3.1.1.6 Harpagoside (HS)

It isa type of iridoid glycoside. HS (**Figure 9**) is considered as the main active component extracted from *Harpagophytumprocumbens* (HP) which is used as anti-inflammatory and analgesic particularly against painful osteoarthritis. The extract wastested to evaluate the antimutagenic activity of HS and HP against mutagenic activity of 1-nitropyrene (1-NPy) that is one of the most abundant nitro-polycyclic aromatic hydrocarbons particularly in diesel exhausts. The results showed that HS significantly reduced the mutagenicity of 1-NPy in pretreatment and particularly in co-treatment. Moreover, HP extract significantly reduced the genotoxicity [19].

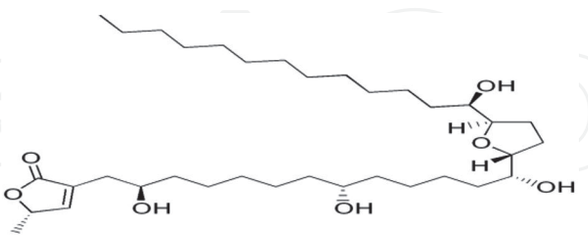


Figure 7.
Acetogenins.

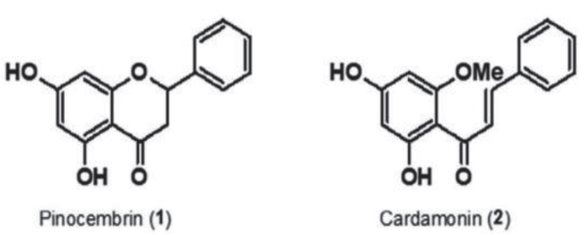


Figure 8.
Pinocembrin and cardamonin.

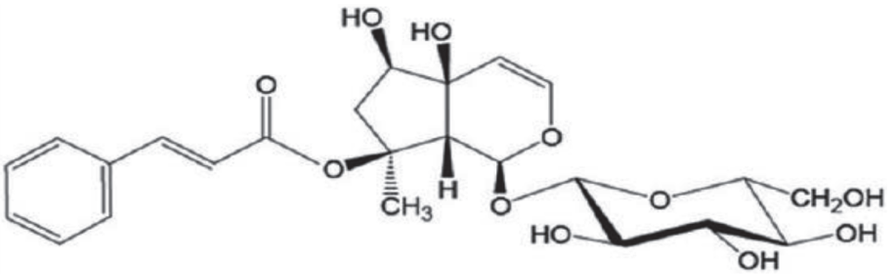


Figure 9.
Harpagoside (HS)

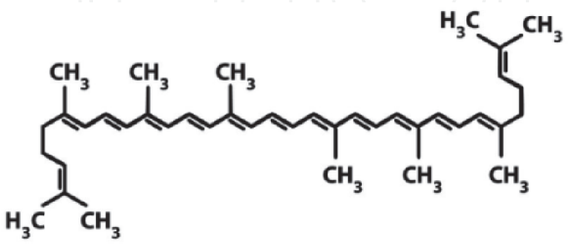


Figure 10.
Lycopene.

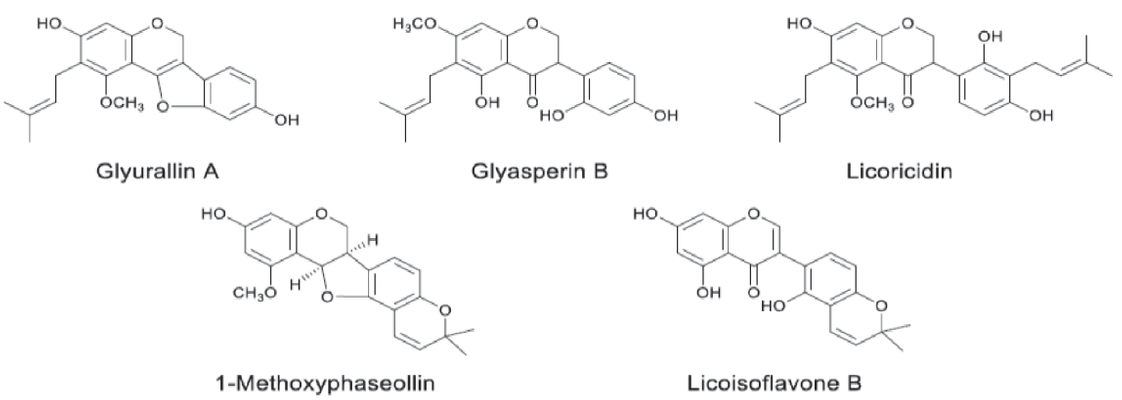


Figure 11.
Glycyrrhiza aspera root extract.

3.1.1.7 Lycopene

Natural oleoresin is rich in lycopene (**Figure 10**), which was obtained from two types of tomato (Zedona and Gironda). The antimutagenic activity of oleoresin was tested against aflatoxin B1 (AFB1), and both varieties had awfully high antimutagenic potential against AFB1 (60–66%) [20].

3.1.1.8 Compounds extracted from Glycyrrhiza aspera *root*

The powdered extract of *G. aspera* root was assayed for antimutagenic activity against N-methyl-N-nitrosourea (MNU) in S. typhimurium TA1535. Five components that were extracted by using ethanol which had antimutagenic activity against MNU were identified as glyurallin A, glyasperin B, licoricidin, 1-methoxyphaseollin, and licoisoflavone B (**Figure 11**). These components were demonstrated to possess an antigenotoxic effect against carcinogenic MNU. So this extract can be used to prevent DNA damage by N-nitrosamines for cancer chemoprevention [21].

3.1.2 Plant extract

3.1.2.1 Date palm *fruit aqueous extract*

It was found that *date palm* extract displays strong antimutagenic activity against ultraviolet (UV) radiation, and mitomycin C-induced mutagenesis, when it was analyzed using *E. coli* RNA polymerase β-based rifampicin resistance assay, but did not show any significant antimutagenesis against ethyl methane sulfonate (EMS) [22].

3.1.2.2 Maytenus ilicifolia *and* Peltastes peltatus *extract*

These two plants are both rich in compounds of the tanninand flavonoid groups and frequently employed in folk medicine. Antimutagenicity was determined against known mutagenic substances such as 4-oxide-1-nitroquinoline, NaN_3, aflatoxin B1, 2-aminofluorene and 2-aminoanthracene, and 2-nitrofluorene using the *Salmonella*/microsome assay. There was a significant decrease in mutagenicity for the tested extract by 75%.The mechanism of antimutagenicity of this extract is still under study [23].

3.1.2.3 Citrus limonum *fruit residues (CLFR)*

Aqueous and acidified methanol extracts of CLFR were evaluated for their total phenolic contents and antioxidant and antimutagenic activities. Antimutagenic potential of the extracts was done by Ames test. The results supported that the extracts from CLFR were mutagenically safe due to its high phenolic content which can act as antioxidant and anitmutagenic [24].

3.1.2.4 Mimosa tenuiflora *(MT) extract*

The genotoxic effect of MT was investigated by using both micronucleus test and Ames test in *Salmonella typhimurium* TA97, TA98, TA100, and TA102, respectively. The results showed that the extract did not induce mutations in any strain. Further studies of toxicity were performed to investigate the use of this plant in the treatment of diseases [25].

3.1.2.5 Albeofructus *(ADA) extract*

It is an extract of *Acanthopanax divaricatus* which possesses antimutagenic activity against direct-acting mutagenic agents through the rapid elimination of mutagenic compounds from the cells before the induction of genetic material damage [26].

3.1.2.6 Anemopsis californica *(AC)*

Although *A. californica* (AC) possesses therapeutic uses, so it could be useful for reducing genotoxic risk generating from ROS-agents exposure and provide protection against poly-cyclic aromatic hydrocarbons which are well known as premutagens and precarcinogens [27].

3.1.2.7 Citrus sinensis *and* Citrus latifolia

The essential oils of *Citrus sinensis* and *Citrus latifolia* showed antimycotic besides antimutagenic and antioxidant activity. Their main components are R-(+)-limonene, α-myrcene, β-thujene, and γ-terpinene [28].

3.1.2.8 Heterotheca inuloides *(HI) extract*

The methanolic extract of HI reduced the mutagenicity of benzo[a]pyrene, norfloxacin, and 2-aminoanthracene. The antigenotoxic properties could be due to the antioxidant properties of component into extract such as catenanes, sterols, polyacetylenes, triterpenes, sesquiterpenes, flavonoids, and flavonoid glycosides [29].

3.1.2.9 Extracts of Acacia salicina

Literatures revealed that this extract displayed potent antioxidant and antimutagenic activities [30]. Also chloroform extract showed antimutagenic effect against both direct- and indirect-acting mutagens, as the extract may act as a blocking agent that is capable of influencing the activities of enzymes engaged in the metabolism of mutagens and carcinogens. Moreover, the tested extract displayed the ability to react directly with the mutagens electrophilic metabolite sand was capable of protecting against oxidative DNA damage [30].

3.1.2.10 Wheat bran

It was reported that wheat bran provides antimutagenic effects that related to the presence of the antioxidant phytic acid. It was demonstrated that phytic acid may intercept carcinogenic azoxymethane, inhibiting it even before it can damage DNA. Moreover, antioxidants included in wheat bran are able tomodulate DNA repair enzymes [31].

3.1.2.11 Vegetables

Activity was displayed by beets, chives, horseradish, onions, rhubarb, and spinach. All cruciferous vegetables showed strong to moderate antimutagenic activities, except Chinese cabbage, which displayed weak activity. Moderate antimutagenicity was found in green beans and tomatoes, whereas weak activities in egg plant, garden cress, many types of lettuces, leeks, mangold, cucumber, pumpkin, radish, and summer squash. However, some vegetables such as *Asparagus*, carrots, fennel leaves, parsley, green pepper, and radishes were not found to display any antimutagenicity [32].

Antimutagenic activity of many vegetable juiceswere earlier studied againstmutagenicity induced by2-amino-3-methyl[4,5-f]-quinoline (IQ), 2-amino-3,4dimethylimidazo[4,5-f] quinoline (MeIQ) or 2-amino3,8-dimethylimidazo [4,5-f] quinoxaline (MeIQx) in S.typhimurium TA98 and TA100 [33].

3.1.2.12 Fruits

Current research all over the world has focused on health protectiveproperties of fruits including antimutagenic potential of different fruittypes and their cultivars. Concerning apple fruit, its antioxidant and radioprotective properties were found to be better correlated with its antimutagenic effect [34]. Recently, copaiba, an exotic

Brazilian fruit, possesses the antimutagenic potential of copaiba powder (dose of 100 mg/kg) showing great reduction of micronuclei [35].

3.1.2.13 Other sources

3.1.2.13.1 Ganoderma lucidum

Ganoderma lucidum was extracted with hot water (GLW) and then partially purified with crude glycoside extract (GLG) and crude polysaccharide extract (GLP). The extract was tested to evaluate the antioxidant and antimutagenic activity. The results showed that the extract has antimutagenic activity due to β-glucan content and antioxidant action due to the presence of high polyphenolic content [36].

3.1.2.13.2 Macro fungus

It was demonstrated that ethyl acetate extract of macro fungus showed the in vitro antimutagenic activity of *Phellinus rimosus*. The activity of the extract against direct-acting mutagens may result from the direct inactivation of mutagens. It is probable that, due to stimulation of the transmembrane export system in bacteria, mutagenic compounds are removed from the cells before they influence the DNA structure [37]. Additionally, in the case of doxorubicin (DXN), the extract of *P. rimosus* may affect the intercalation of mutagens to genetic material.

3.2 Synthetic antimutagenic agents

Synthetic antimutagens is another important trend in the area of antimutagenicity research.

3.2.1 Steroidal hormonal molecules

Bile acids have either a co- or an antimutagenic activity toward various direct- and indirect-acting mutagens [38]. It was reported that steroidal hormones could inhibit the genotoxicity of both direct- and indirect-acting mutagens [39]. For example, both ethinyl oestradiol and mestranol (**Figure 12**), which are synthetic derivatives of 3-estradiol largely used in contraceptive pills, are strong mutagenic inhibitors acting at nanomolar concentrations [39].

3.2.2 Gallic acid

It could act as a nucleophile to scavenge the electrophilic mutagens. It was implied that gallic acid (**Figure 13**) can bind or insert into the outer membrane

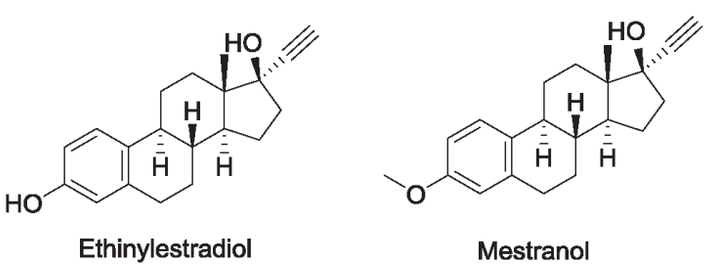


Figure 12.
Steroidal hormonal molecules

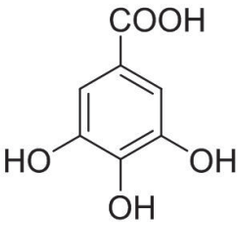


Figure 13.
Gallic acid.

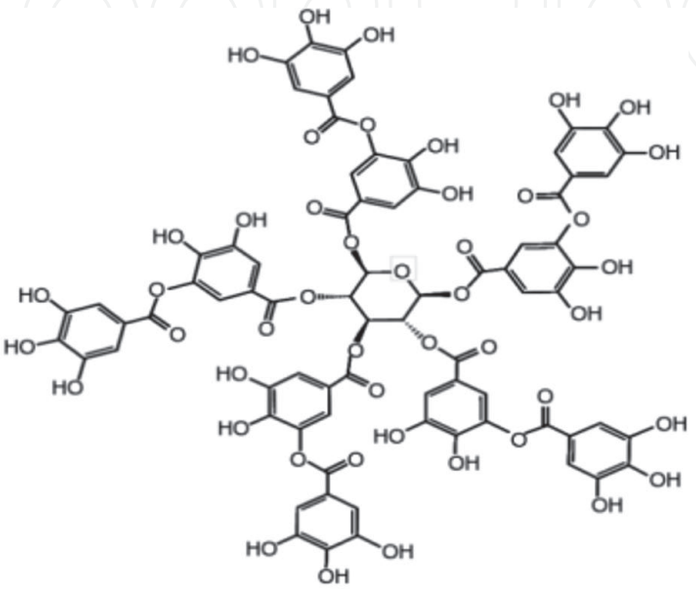


Figure 14.
Tannic acid.

transporters leading to the blockage of a mutagen that was transferred intothe cytosol [40]. One of the mutagenic substances that gallic acid affects is NaN3. It is widely used in agriculture, industry, and medicine, but it is a highly toxicsubstance. If sodium azide is found in the intracellular milieu, azide ions bind Fe3þ in hemoglobin and inhibit the respiratory chain of metabolism [41].

3.2.3 Tannic acid

The anticlastogenic effect of tannic acid (**Figure 14**) was studied *in vivo* in the mouse micronucleus test. Moreover, the antimutagenic effect of tannic acid was investigated *in vivo* in the mouse spot test using male PW and female C57BL/10 mice. The results showed that tannic acid can act as an anticlastogen and antimutagen in vivo [42].

3.2.4 Synthesized β- aminoketones

Theantigenotoxic potential of two newly synthesized β-aminoketones such as2-{(4-bromophenyl)[(4-methylphenyl) amino] methyl} cyclohexanone and 2-{(4-chlorophenyl)[(4-methylphenyl) amino] methyl} cyclohexanone compounds was tested against the mutagenN-methyl-N-nitro-N-nitrosoguanidine (MNNG), acting by DNAmethylation (**Figure 15**) [9]. The antimutagenic potential of these compounds may be related to the inhibition of the production of O6-methylguanine,

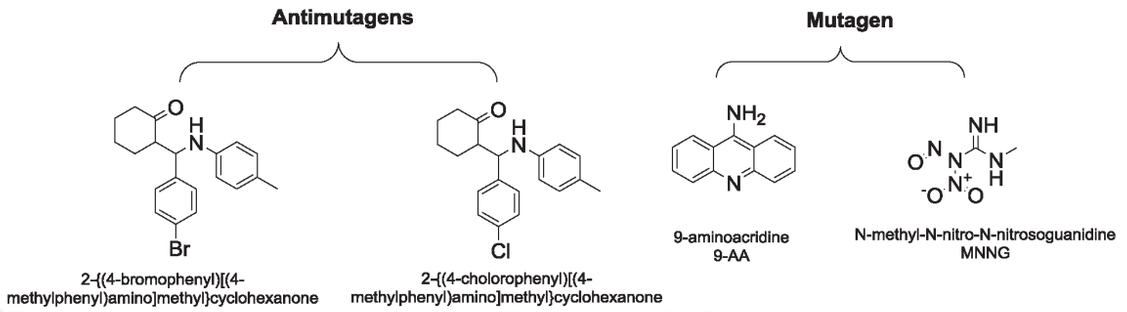


Figure 15.
β-Aminoketones and mutagens.

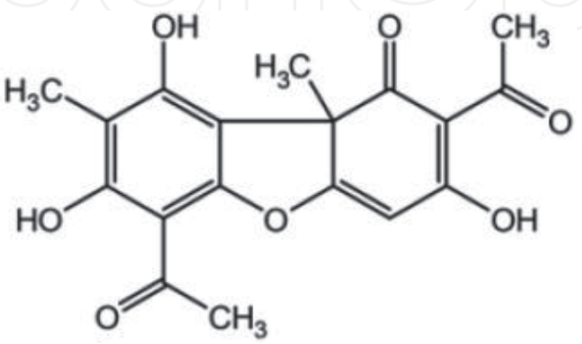


Figure 16.
Usnic acid.

a product of MNNG that is related to its mutagenic effect. Both compounds also abolished mutagenesis induced by 9-AA that binds to DNA noncovalently by intercalation [43].

3.2.5 Phenolic agents

This category of antimutagenics acts against mutagens via either intracellularor extracellular mechanisms [44]. The extracellular mechanism showed interference with the cytochrome P450-mediated metabolismof these mutagens and the interaction with active mutagenicmetabolites [8]. Moreover, the antimutagenic potency of these compounds may be relatedto DNA protection from mutagens presenting electrophilicproperties [8].

Hydroxyphenyliminoligands and their metal complexes [Cu(II), Co(II), Ni(II) and Mn(II) complexes] of usnic acid (**Figure 16**) which is isolated from *Usnea longissima*, were synthesized by Schiff base method with *O-*, *P-,* and *M-*aminophenol compounds to determine their antimutagenic activity against different bacteria species. The results showed that the Co and Mn complexes of the ligands possess potent antimutagenic activity [45].

New polymeric microspheres containing azomethine were designed and synthesized to evaluate their antimutagenic activity against NaN_3, among of them; a new polymeric microspheres containing azomethine (**Figure 17**) which contains R = CH_3 had potent antimutagenic effect against NaN_3 [46].

Chitosan derivatives containing quaternary ammonium groups and di (tertbutyl) phenol (TBPh) (**Figure 18**) in the polymer side chain improved the antimutagenic efficiency of the polymer from 48 to 93% [47].

Hydrazone derivatives were synthesized to study their antioxidant and antimutagenic activity against 4-NPD and NaN3 in *S. typhimurium* TA98 and TA100, respectively, among of them; the hydrazone derivative (**Figure 19**)

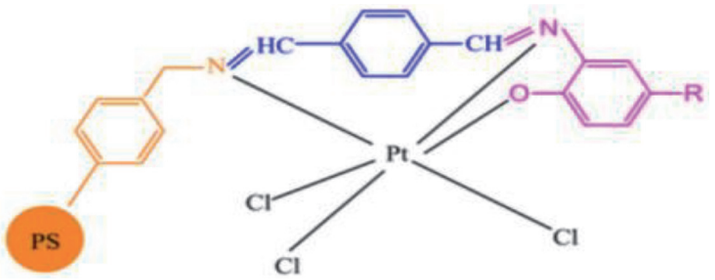


Figure 17.
New polymeric microspheres containing azomethine.

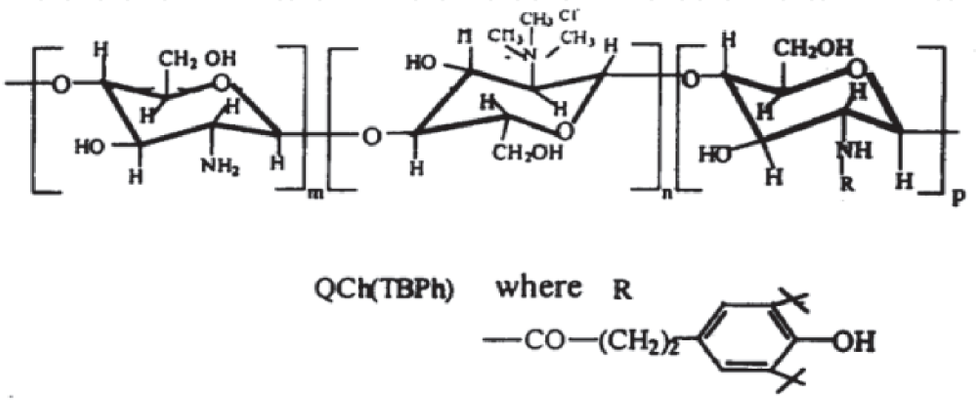


Figure 18.
Chitosan derivatives containing quaternary ammonium groups.

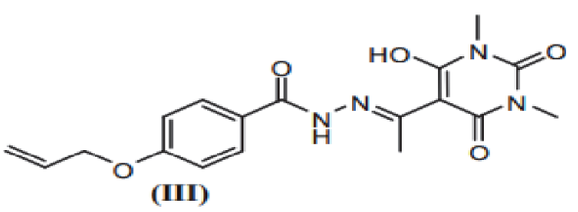


Figure 19.
Hydrazone derivatives

had high antimutagenic activity. The strongest antimutagenic activity was observed at 5 mg/plate concentration against *S. typhimurium* TA100 strain [48].

3.2.6 Xanthones

The potential antimutagenic of xanthonesis attributed to different mechanisms, such as the rapid elimination of mutagens from bacteria; the interaction between antimutagens and the reactive intermediates of mutagens; and the influence on microsomal enzymes against direct mutagen 4-nitroquinoline-N-oxide (NQNO) (**Figure 20**) [49].

3.2.7 Indols

Novel polymeric-Schiff bases including indol (L1, L2, L3) (**Figure 21**) exhibited the antigenotoxic properties against sodium azide in human lymphocyte cells by micronuclei (MN) and sister chromatid exchange tests [50].

A series of indolizine derivatives have been synthesized to determine their anti-mutagenic activity, the indolizine derivative (**Figure 22**) had the highest activity [51].

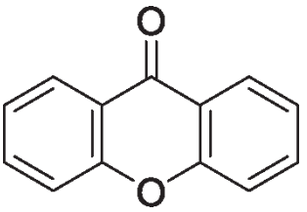


Figure 20.
Xanthone.

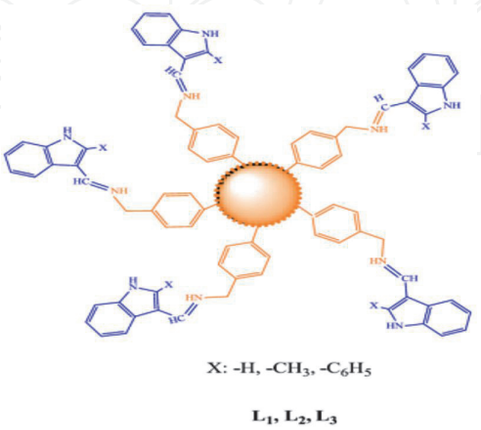


Figure 21.
Novel polymeric-Schiff bases.

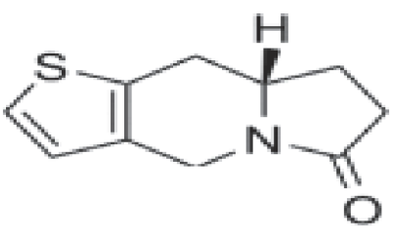


Figure 22.
Indolizine.

3.2.8 Organoselenium

Scientists demonstrated that this series of compounds are protected against genotoxicity and oxidative stress induced by an indirect-acting mutagen CP [52]. This is attributed to effect of CP on DNA through its alkylating properties and free radicals production [53].

3.2.9 Bichalcophenes

The novel bichalcophenes significantly decreased the mutagenicity induced by two mutagens, namely, NaN_3 and BP [54]. It was found that the antimutagenic potential of the compounds could be attributed to their antioxidant activity [55].

3.2.10 Others

New zerumbone-bicarbonyl analogues were synthesized to determine their antimutagenic activity against *Salmonella* tester strains. Zerumbal (**Figure 23**) had significant higher antimutagenic activity than zerumbone [56].

Two newly synthesized oxadiazoles: 1,3-bis(5-benzylthio-1,3,4-oxadiazol-2-yl) benzene (M1) and 1,4-bis(5-benzylthio-1,3,4-oxadiazol-2-yl) benzene (M2) (**Figure 25**) were synthesized and studied in *Salmonella typhimurium* strains TA97, TA100, TA102 and TA1537 in the presence and absence of S9mix. The antimutagenicity of M1 and M2 against H_2O_2, NaN_3, and 4-nitro-o-phenylene diamine (NPD) using the tester strains, was also investigated. The two compounds were found to be nonmutagenic [58].

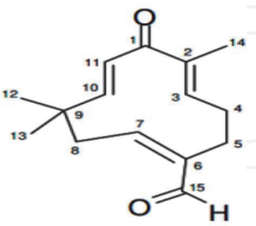


Figure 23.
*1,4-Dihydropyridines (1,4-DHP) (**Figure 24**) possessed antioxidant and antimutagenic activities. The compounds modified the activity of DNA repair enzymes, to protect the DNA in living cells against peroxynitrite-induced damage [57].*

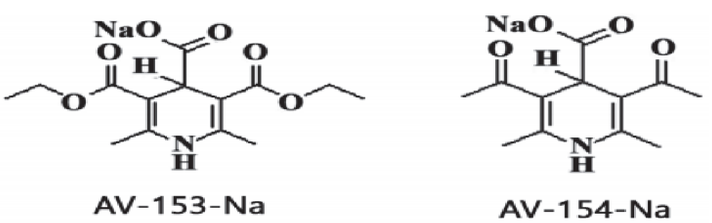


Figure 24.
1,4-Dihydropyridines (1,4-DHP) derivatives.

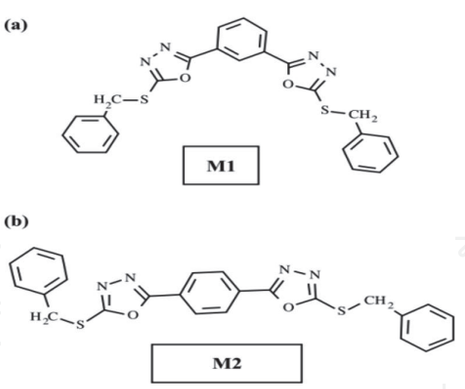
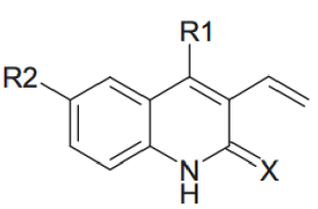
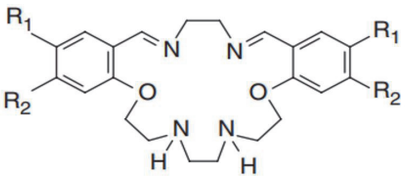


Figure 25.
Oxadiazole derivatives.



1c R1=C_6H_5 R2=Cl X=O; **1d** R1=C_6H_5 R2=NO_2 X=O

Figure 26.
Dihydrothienoquinoline derivatives.



1 $R_1 = R_2 = H$
2 $R_1 = NO_2$, $R_2 = H$
3 $R_1+R_2 = CH=CH-CH=CH$

Figure 27.
Azacrown ether Schiff bases.

Dihydrothienoquinoline derivatives were designed and synthesized to evaluate their antimutagenicity using Ames test. Several compounds showed good antimutagenicity. The results for compounds (**Figure 26**) were found to be statistically significant (P = 0) [58].

A series of novel azacrown ether Schiff bases have been synthesized, and they were investigated for their antimutagenic activities using the spot test and Ames test using strains TA1535, TA100, and TA97a of *Salmonella typhimurium*. The results showed that compounds 1 and 2 (**Figure 27**) were antimutagenic [59].

Conflict of interest

The authors declare no conflict of interest.

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