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# Protective Effects of Natural Products and Their Derivatives on Genetic Material: A Critical Review

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**Abstract:** Although treatment with natural products and the substances derived from them has gained much attention, it is important to know the genomic safety of these substances prior to their use in humans. The present review aims to present the current knowledge on the genoprotective effects and possible mechanism of actions of natural compounds. Therefore, an up-to-date search was conducted using known databases such as PubMed, ScienceDirect, and Clinicaltrials.gov. For the investigation of genotoxic/genoprotective activity of these substances, comet or micronucleus assay were frequently used models applied through eukaryotic test systems, bacterial strains, cultured animal cells or tissues (e.g., mice, rats) but also human by using oxidizing or carcinogenic agent-induced DNA damage capacity. Findings suggest that several extracts, including those from medicinal plants, marine algae or their preparations, antioxidants such as quercetin, retinoids, resveratrol, hyaluronic acid, carnosol, rosmarinic acid, and naringin have shown genoprotective effects in various test systems. Antioxidant, anti-inflammatory, mitogenic, reduction of DNA strand breaks and DNA lesions, formation of micronucleus, and chromosomal aberrations were the observed mechanisms of action of genoprotective substances. In conclusion, this review highlights the importance of natural products, especially dietary antioxidants, which can be safely used for the treatment of various diseases.

**Keywords:** Antioxidants; extracts; genoprotective effects; Comet assay; DNA damage. 

## 1. Introduction

Studies related to genotoxicity and mutagenicity are essential in the identification of adverse effects of drugs, cosmetics, industrial compounds, agrochemicals, food additives, natural toxins, and nanomaterials for

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regulatory purposes. In this context, evaluation of mutagenicity or genotoxicity provides an adequate safeguard for a therapeutic substance and reduces the risks of cancer in humans and other animals [1]. In cancer, besides a number of treatment strategies, including the new classes of these drugs, there is still a challenge in the management concerning how to improve treatment efficacy and to diminish adverse effects. In this respect, bioactive substances of natural origin are constantly developed, characterized, and checked by applying various test models [2]. It is important to stress that risk assessment is crucial prior to administering any therapeutic compound into an organism.

Although natural products are important for drug discovery, and herbal compounds are widely used to treat different diseases, the number of reports exploring their clinical efficacy and safety is relatively small [3-5]. Moreover, integrity and stability of genetic materials (e.g., DNA, RNA) are essential to an organism's health and survival [6]. Some of these natural products or their derivatives may be promising for the development of dietary supplements or drugs [7-10]. In general, natural products contain a variety of components which may be useful in protecting against cellular damage caused by mutagens [11-14]. For example, dietary components and supplements such as coffee [15,16] and green tea [17-19], phytochemicals [20-24], antioxidants [25,26], microbial metabolites [27], and synthetic compounds obtained from natural products [28] have antioxidant and genoprotective effects in humans and experimental animals. Several studies have shown potential antigenotoxicity in a variety of fruits, polysaccharides [29], plants, vegetables, and natural resins [30]. Because of wide interest in the phytochemical pharmacological activities of natural products and their derivatives, this review focuses on evaluating the genoprotective effects of natural products and their derivatives on the basis of published reports. For this purpose, recent relevant references, dealing with this subject have been acquired from different databases such as PubMed, ScienceDirect, and Clinicaltrials.gov. This review should be a useful resource of information and a benefit to researchers in the field.

## 2. Materials and Methods

### *2.1. Search Strategy*

An up-to-date search (through January 2021 of known databases including PubMed, ScienceDirect, and Clinicaltrials.gov using the keywords 'genoprotective effect' or 'antigenotoxic' paired with 'antioxidants', 'medicinal plants', 'natural or herbal products', or 'phytochemicals' was conducted; no restrictions were imposed in the search strategy. The inclusion and exclusion criteria are given below.

### *2.2. Inclusion and Exclusion Criteria*

Inclusion criteria were: (1) reports that discuss genoprotective effects of antioxidants, medicinal plants, natural/herbal products, or phytochemicals, (2) reports with or without explained a proposed mechanism of action, test concentration or dose, route of administration, test system or test model, and (3) reports on crude extract, fractions, isolated substances or their derivatives of natural origin, such as from medicinal plants, bacteria, fungi, algae, and marine substances. On the other hand, exclusion criteria included (1) titles, abstracts, or contents not meeting the inclusion criteria, (2) data duplication in the databases, and (3) data that were non-related to the searched keywords.

## 3. Results and Discussion

### *3.1. Findings*

The search found 599 reports in the above-mentioned databases, with 78.3 and 21.7% reports from ScienceDirect and PubMed, respectively. No reports were found in the Clinicaltrials.gov database. After exclusion based upon above mentioned criteria, a total of 155 (25.9%) reports have been included in this study.

Findings are classified in crude extracts and preparations, isolated substances, and synthetic derivatives. Extracts are readily obtained and cost-effective, but the compositions can vary widely. Isolated substances and synthetic derivatives are pure compounds, but they are likely to be unobtainable or very expensive.

*3.2.1. Crude Extracts and Preparations*

The comet assay (single-cell gel electrophoresis) represents a simple method by which the breakdown of deoxyribonucleic acid (DNA) in eukaryotic cells can be measured. Cells embedded in agarose on the slide are lysed with detergent and high salt concentration to form nucleoids containing supercoiled loops of DNA linked to the nuclear matrix. Electrophoresis at basic pH results in structures resembling comets, where the intensity of the comet tail in relation to the head reflects the number of DNA breaks and become free to extend towards the positive end of the electrophoretic cell (anode) since DNA is negatively charged [31,32]. This assay is a truly reliable method with a multitude of possible applications [33]. It can be applied in testing new substances for their genotoxicity/genoprotective effects, for monitoring environmental contamination with genotoxins, human biomonitoring and molecular epidemiology, and fundamental research in DNA damage and repair [29,30,34]. By applying this test model, it is possible to recognize specific kinds of damage of DNA and repair DNA lesions [31].

Oxidative stress is an active area of research on the toxic mechanisms of wide varieties of substances, and identification of antioxidant agents that might be helpful for human health [35]. Numerous ancient texts from Chinese traditional medicine, Ayurveda and Siddha, and Japanese traditional medicine have indicated that natural products have promising effects against oxidative stress and inflammation [36]. Cellular antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH), glutathione *S*-transferase (GST) activity, as well as oxidative damage including lipid peroxidation, protein and DNA oxidation, are used as biomarkers for oxidative stress, while micronucleus (MN, also called small nucleus) test is used for the evaluation of chromosomal damage and as an indication of genotoxicity [37]. A number of dietary components [38-51], medicinal plants [52-88] or other natural extracts/preparations [89-103] have been found to act against oxidative stress-induced DNA damage in various test systems.

Radiation, including X-rays, can cause increased oxidative stress, activation of the inflammatory response, and accumulation of DNA damage, among other effects. Plant extracts and natural compounds or their derivatives can protect or mitigate the harmful effects caused by radiation in different experimental models. Therefore, photoprotective products based on natural compounds are continuously being developed, and there is an increasing expansion of research in this field [104]. Reports suggest that plant extracts [52,61,71,105-107] or other natural products [44] can act against radiation-induced genotoxic effects on cells/ tissues derived from plants and animals.

MN forms whenever a chromosome or a fragment of a chromosome is not incorporated into the daughter nucleus during cell division. MN formation is a sign of genotoxic events and chromosomal instability and is commonly observed in cancer cells. It also indicates genomic damage that can increase the risk of developmental or degenerative diseases [108]. The MN test has been applied for more than three decades to investigate an early warning of genotoxic/genoprotective properties of a wide variety of substances [109]. A number of medicinal plants [14,56,110-113] or other natural extracts [89,114-116] have been found to reduce MN formation in test systems.

On the other hand, chromosomal aberration (CA) or mutation is a missing, extra or an irregular portion of chromosomal DNA. CA can occur in a typical number of chromosomes or a structural abnormality in one or more chromosomes [117]. *Armoracia rusticana*, *Ficus carica* and *Zea mays* [105], *Hemidesmus indicus* [118], olive leaf [119], bee-pollen or propolis [115], *Bryoria capillaris* [110], *Orthosiphon stamineus* [14], *Nigella sativa* [113], and *Parkinsonia aculeata* [120] were found to reduce the CA in test systems.

Mutation is the alteration of the nucleotide sequence of genome that results from errors during DNA replication or other types of damage to DNA caused by exposure to radiation or carcinogens [121]. Studies have shown that the ethanol crude extract of *Rhoeo discolor* [122], fruit extract of *Rosa roxburghii* [123], oils of fruit and leaf extract of *Fagus orientalis* [124], *Saraca asoca* bark extract [125], *Cladosporium velox* TN-9S [89] and *Opuntia microdasys* extracts [97] have non- or anti-mutagenic effects in test systems. In addition to genoprotective studies, septilin (a polyherbal drug formulation) has been reported to have a clastogenic effect in Swiss mice [116], whereas hydroethanolic extract of *Juniperus communis* inhibited the mitogenic effect of ethanol on *Allium cepa* meristem [126]. In Table 1 are listed crude extracts or preparations that have activity against genotoxic effects of oxidizing, antineoplastic, radiation, or other toxic agents in various test systems.

**Table 1**. Genoprotective effects of crude extracts or preparations

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Acacia salicina* leaf aqueous, methanol, and ethyl acetate extracts | 50, 250, and 500 µg/plate | *Salmonella typhimurium* and human lymphoblast cells | Comet assay: benzo[a]pyrene and $H_2O_2$-induced DNA damage | Ethyl acetate and methanol extracts decreased DNA damage profile | [166] |
| *Acalypha fruticosa* aqueous and methanolic extracts | 50 µg | pBR322 | Comet assay: UV-photolyzed and $H_2O_2$-induced DNA damage | Reduces oxidative DNA damage | [61] |
| *Aegle marmelos* fruit methanol, acetone and aqueous extracts | 50, 100, 150 and 200 µg/assay | *Escherichia coli* and human peripheral blood lymphocytes | SOS chromotest and comet assays | Antigenotoxic activity | [83] |
| *Aegle marmelos* leaves extracts | 10 mg/mL | Fish blood | Micronucleus assay | Antigenotoxic activity | [84] |
| *Agaricus bisporus* (fungus) | - | Raji cells (a human lymphoma cell line) | Comet assay: $H_2O_2$-induced oxidative damage | Decreases oxidative DNA damage | [91] |
| *Agaricus blazei, Cordyceps sinensis, Coriolus versicolor, Ganoderma lucidum, Grifola frondosa, Lentinula edodes.* Immune Assist from six mushroom extract | 250, 500 and 1000 µg/mL | Human peripheral blood cells | Comet assay: $H_2O_2$ induced DNA damage | Significant antioxidant and oxidative DNA damage effects | [90] |
| *Amaranthus viridis* aqueous, methanol, chloroform and hexane extracts | 8, 16, 32 and 64 µg/mL | Human mononuclear cells | Alkaline comet assay | Methanol extract showed DNA protective effect | [101] |
| *Allium sativum* extract | 170 µg/mL | Human RD cells | $CdCl_2$, 4-nitroquinolone-1 oxide and γ-radiation induced mutagenicity | Antioxidant and reparative activities | [52] |
| *Armoracia rusticana*, *Ficus carica* and *Zea mays* | - | Meristematic cells of *Vicia faba* and marrow cells of mice | Gamma-ray induced DNA damage | Decreases the frequency of chromosome aberrations (CA) | [105] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Azadirachta indica* | 100 and 200 mg/kg | Rats | Arsenic intoxication | Significant reduction in the frequency of MN-induced apoptosis and oxidative stress | [112] |
| *Bacopa monniera* aqueous extract | 50 mg/kg (i.p.) | *Swiss* mice (n = 6) | Nicotine-induced toxicity | Antioxidative effect (restored superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), alkaline phosphatase (ALP), glutathione *S*-transferase (GST) levels); reduced the frequency of micronuclei (MN) by decreasing the incidence of micronucleated polychromatic erythrocytes (MNPE) | [56] |
| *Bryoria capillaris* aqueous extract | 5, 10, 25, 50 and 100 µg/mL | Cultured human lymphocytes | Alkaline comet assay | Reduces the frequency of CA and MN formation in a dose-dependent manner | [110] |
| *Camellia sinensis* (black tea) tea extract | 10 or 25 mg/L | Jurkat T-cell line | Iron-induced oxidation | Increases GPx levels; decreases oxidative DNA damage (single strand breaks) | [39] |
| *Camellia sinensis* (black tea) tea extract | 0.005–500 µg/mL | Human lymphocytes | Comet assay: $H_2O_2$ or gamma-rays (2 Gy dose) induced DNA damage | Prevented strand DNA break or DNA damage at lower doses | [44] |
| *Camellia sinensis* (green tea) extract | 10 mg/L | Jurkat T-cell line | Iron-induced oxidation | Decreases oxidative DNA damage (single strand breaks) | [38] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Camellia sinensis* (green tea) extract | 0.005, 0.01 and 0.05 %w/v | Human peripheral lymphocytes | Comet assay: $H_2O_2$-induced DNA damage | Significant DNA damage preventive capacity at higher concentration | [42] |
| *Camellia sinensis* (green tea) extract | 200 mL of 1.5%, w/v | Human (n = 16) lymphocytes | - | Causes a significant increase in human DNA repair enzyme oxoguanine glycosylase 1 (after 1-2 h) and heme oxygenase-1 (after 7 days) | [41] |
| *Camellia sinensis* (green tea) extract | 1.3–6.5 mg/kg/day for 5 days | Hepatocytes, colonocytes and lymphocytes of rats (n = 5) | Comet assay | Lesser extent of oxidative DNA damage preventive capacity | [167] |
| *Ceratonia siliqua* extracts | 32.5–280 µg/mL | Murine leukemia cells L1210 | Comet assay: $H_2O_2$ - mediated DNA damage | Antioxidant effect; decreased DNA damage profile | [72] |
| *Citrullus colocynthis* fruit extract | 0.5–3.5 mg/mL | Mouse bone marrow cells | Micronucleus assay: cyclophosphamide-induced DNA damage | Reduces oxidative DNA damage | [68] |
| *Cladosporium velox* TN-9S | 125–500 µg/mL | *Channa punctatus* (fish) & *Salmonella typhimurium* $His^-$ strain | Micronucleus assay | Antioxidant, genoprotective and non-mutagenic effects | [89] |
| *Cortex moutan* and *Rhizoma dioscoreae* aqueous extracts | - | Human DNA | Comet assay: $H_2O_2$-induced DNA damage | Decreases DNA stand break | [58] |
| *Crocus sativus* stigmas aqueous extract & crocin | 5, 20 and 80 mg/kg & 50, 200, and 400 mg/kg (i.p.) | *Swiss* mice | Comet assay: methyl methanesulfonate-induced DNA damage in multiple organs | Extract reduced DNA damage at 5 mg/kg, while crocin reduced DNA damage in a dose-dependent manner | [168] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| Cucurbitaceae (*Momordica dioica, Citrullus colocynthus, Cucumis melo var. agrestis*) seeds (70% aqueous methanol) extracts | 5, 10 and 20 mg/mL | PBR322 DNA plasmid protection assay | Comet assay: $H_2O_2$ - mediated DNA damage | Decreased oxidative DNA damage | [73] |
| *Curcuma vamana* | - | - | $H_2O_2$/UV-induced oxidative DNA damage | DNA protection capacity | [71] |
| *Cyperus rotundus* aerial parts extracts: aqueous, ethyl acetate, methanolic and total oligomer flavonoids | 50, 200 and 500 µg/assay | *Escherichia coli* | SOS chromotest assay | Antigenotoxic and antioxidant activities | [103] |
| *Daedaleopsis confragosa* (fungus) hot water extracts of fruiting bodies and mycelia | - | Leukocytes | Comet assay: $H_2O_2$ - mediated DNA damage | Significant protective activity against DNA damage | [99] |
| *Daphne gnidium* leaves methanol extract | 44, 88 and 176 mg/kg | Mouse (n = 5) blood and kidney cells | Comet assay: methyl methanesulfonate-induced DNA damage | Protected cellular DNA from oxidative stress | [169] |
| *Detarium microcarpum* fruit extract | 500, 1000 and 2000 mg/kg | Liver cells of NMRI female mice | Comet assay: cyclophosphamide-induced DNA damage | Induction of the expression of antioxidant and DNA repair enzymes | [74] |
| *Dianthus carmelitarum* aqueous extract | 100, 250 and 500 µg/mL | Human foreskin fibroblast cells | Alkaline comet assay: $H_2O_2$-induced DNA damage | Reduced $H_2O_2$-induced DNA damage in a concentration dependent manner | [100] |
| *Diospyros kaki* fruit extracts | 50 µg/mL | Human leukocytes | Comet assay | Inhibited DNA damage induced by $H_2O_2$ | [49] |
| *Echinacea purpurea, Origanum vulgare, Rosmarinus officinalis*, and *Salvia officinalis* extracts | 5–1000 µg/mL | Caco-2 cells exposed to 24 h | Comet assay: $H_2O_2$-induced DNA damage | Increases reduced GSH content; reduces oxidative DNA damage | [55] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Echinacea purpurea*, four plant extracts-grapeseed polyphenols, olive leaf extract and bearberry | - | U937 cells | Comet assay: $H_2O_2$ and *tert*-butylhydroperoxide-induced DNA damage | Grapeseed polyphenols and bearberry showed strong protective effects against oxidative DNA damage | [54] |
| *Euterpe oleracea* fruit | 3.33, 10.0 and 16.67/kg body weight | Swiss albino mice | Micronucleus assay and alkaline comet assay | Subacute treatment provided greater efficiency in protecting against doxorubicin -induced DNA damage in liver and kidney cells | [46] |
| *Fagus orientalis* fruit and leaf extract oils | - | *Allium cepa*, *Vicia faba*, *Triticum aestivum*, *Arabidopsis thaliana*, and marrow cells of Vistar rats | - | Anti-mutagenic effects | [124] |
| *Ficus palmata* bark (aq.) and leaf (methanol) extracts | 2.5–20 µg/mL | Plasmid DNA | Ferric chloride induced DNA damage | Prevention of oxidative DNA damage | [70] |
| *Fraxinus angustifolia* leaves and stem bark ethanol extracts | 25, 50 and 100 µg/mL | *Salmonella typhimurium* | Ames and umu test | Antimutagenic and antigenotoxic effects | [80] |
| *Ganoderma lucidum* (fungus) | - | - | Comet assay | Potent antioxidant and antigenotoxic effects | [95] |
| *Ganoderma lucidum* (fungus) aqueous extract of dried fruit bodies | 0.0001-0.1% | Lymphocytes of healthy female (n = 2) | Comet assay | Genoprotective effect at 0.0001% w/v | [170] |
| *Gentiana lutea* methanol extracts | 0.03125-2.5 mg/mL | HepG2 cells and *Salmonella typhimurium* | Alkaline comet and SOS/umuC assay assays | Inhibition of genotoxicity in both models | [85] |
| *Ginkgo biloba* leaf ethanol extract and *in vitro* simulated human digestion | 1.2, 2.4, 12 and 24 µg/mL gallic acid equivalents | HT-29 cells | Comet assay | Antioxidant and antigenotoxic activities persisted after *in vitro* digestion | [155] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Glycyrrhiza glabra* methanol extract | 5.96 to 191 µM | *Escherichia coli* and human peripheral blood lymphocytes | SOS chromotest and comet assays | Modulatory effect on genotoxicity | [82] |
| *Gracilaria gracilis* and *Fucus vesiculosus, Ulva rígida.* Diet containing marine macroalgae | 30 days treatment | *Sparus aurata* (fish) | Extractable nuclear antigen and comet assay: cyclophosphamide-induced genotoxic challenge test | Reduces DNA strand breaks, chromosomal lesions, and reducing oxidative DNA damage | [6] |
| *Gymnema montanum* ethanol leaf extract | 200 µg/mL | Human peripheral blood lymphocytes and HL-60 cell line | Comet assay: $H_2O_2$ and methyl methanesulfonate induced DNA damage | Decreases sub-G1-DNA content in cell cycle analysis and apoptotic frequencies | [62] |
| *Hemidesmus indicus* root hydroalcoholic extract | 10 and 25 µg/mL | lymphoblastic leukemia cell line | - | Prevented extracellular and intracellular events involved in DNA damage | [171] |
| *Hemidesmus indicus* root ethanol extract | 2 to 32 µg/mL | Cultured human lymphocyte | Comet assay: cisplatin-induced DNA damage | Significant reduction in frequencies of sister chromatid exchanges, CA and micronucleated binucleate cells (MNBC) at 4 and 8 µg/mL | [118] |
| *Hibiscus sabdariffa* aqueous extract | 0–1000 ng/mL for 24 h exposure | Murine bone marrow (BMCs) cells | Comet assay: $H_2O_2$-induced DNA damage | Increases GSH and SOD levels; decreases reactive oxygen species (ROS) level and oxidative DNA damage profile | [69] |
| *Hibiscus sabdariffa* aqueous extract | 13 mg gallic acid equivalents/g dry weight | Human lymphocytes. | Comet assay | Prevented DNA damage | [77] |
| *Juniperus communis* hydroethanolic extract | 5–100% v/v | *Allium cepa* | Comet assay | Inhibited the mitogenic effect | [126] |
| *Koelreuteria paniculata* leaf methanol extract and hexane fraction | - | pUC18/calf thymus | Fenton's reagent induced DNA damage | Both showed antioxidant and DNA protective effects | [63] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Lactuca sativa* hydroalcoholic extract of green leaf | 50 and 400 µg/mL | N2a cells | Comet assay: single cell gel electrophoresis | Extract at 400 µg/mL reduced DNA fragmentation | [172] |
| *Melissa officinalis* aqueous and methanol extracts | 100, 250 and 500 mg/kg | CF-1 male mice | Alkaline comet and micronucleus assays | Antigenotoxic and antimutagenic effects | [86] |
| *Nigella sativa* seed extract | 10, 50 and 250 µg/mL | PC12 cells | Alkaline comet assay: ischemic insult | A dose-dependent significant decrease in DNA damage profile | [140] |
| *Nigella sativa* oil | 2 mL/kg/day for 2 weeks | Adult female Sprague-Dawley rats | Micronucleus assays | Reduces MN incidence, DNA damage and CA frequency | [113] |
| *Olea europaea* leaf extract | 50, 100 and 200 mg/L | Cultured human blood cells | Permethrin-induced oxidative damage | Increases antioxidant capacity; reduces sister chromatid exchange and CA in a dose-dependent manner | [119] |
| *Olea europaea* leaf extract | 0.125, 0.5 and 1 mg/mL | Human (n = 6) leukocytes | Comet assay | Reduces DNA damage (attenuate formation of DNA lesions) at smaller concentrations | [173] |
| *Opuntia microdasys* extracts | 0.03-30 mg/mL | *Allium cepa* | Comet assay; $H_2O_2$ - mediated DNA damage | Anti-mutagenic effect | [97] |
| *Origanum vulgare* ethanol extract | 50, 100, 200, or 400 mg/kg for 7 days | Mouse bone marrow cells | Micronucleus assay: cyclophosphamide-induced DNA damage | Reduces the number of MNPE and normalized the mitotic activity in a dose-dependent manner | [111] |
| *Origanum vulgare* aqueous extract | 2.5 and 5% | DNA biosensor | Square wave voltammetry (SWV) technique | Genoprotective and antioxidative effects | [102] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Orthosiphon stamineus* 50% ethanol extract | 250, 500 and 1000 mg/kg | Bone marrow cells of Bab/c mice | Micronucleus assay | Modulated MNPE/PMNE ratio, mitotic index (MI), and CA values in mice, suggesting genoprotective potential | [14] |
| *Panax quinquefolius* (American ginseng) | 200 mL of infusion | Human (n = 7) lymphocytic | Alkaline comet assay: $UV_B$ irradiation induced DNA damage | Protected cellular DNA from oxidative stress | [107] |
| *Panax quinquefolius* and *Panax ginseng* (American and Asian ginseng) | - | Human (n = 3) lymphocytes | Comet assay: $H_2O_2$-induced DNA damage | Reduces DNA damage score | [59] |
| *Paullinia cupana* hydro-alcoholic extract | 0.5, 1, 5, 10 and 20 mg/mL | Embryonic fibroblast cultured (NIH-3T3) cells | Sodium nitroprusside induced genotoxicity | Both showed antioxidant and DNA protective effects | [66] |
| *Parkinsonia aculeata* leaf extract | 0.1–2.0 ppm | *Allium cepa* | Maleic hydrazide induced chromosomal aberration assay | Increases MI and great reduction in CA | [120] |
| *Phyllanthus orbicularis* extract | 10, 100 and 100 µg/mL | Plasmid DNA | Radiation exposure | Protective effect against DNA damage induced by environmental sunlight radiation | [174] |
| *Pinus banksiana* and *Picea sitchensis* extracts | 10 and 30 µg/mL | Human Jurkat T cells | Comet assay: $H_2O_2$-induced DNA damage | Increases GSH and CAT levels; decreases interleukin-2 (IL-2) production and oxidative DNA damage | [57] |
| *Pinus halepensis* aqueous methanol extract | 100, 250, 350 and 500 µg/mL | pBluescript M13 (+) plasmid DNA | DNA damage generated by $H_2O_2$ and UV radiations | DNA protective effects | [78] |
| *Polyscias filicifolia* methanolic extracts | 0.31-10 mg/L | *Salmonella typhimurium* | SOS/umuC assay assays | Antigenotoxic effect | [88] |
| *Punica granatum* aqueous leaf extracts | 400, 600 and 800 mg/kg | Swiss albino mice | Bone marrow micronucleus test | Antioxidant and antigenotoxic potential | [50] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Quercus ilex* aqueous methanol extract | 100, 250, 350 and 500 µg/mL | pBluescript M13 (+) plasmid DNA | DNA damage generated by $H_2O_2$ and UV radiations | DNA protective effects | [78] |
| *Rhoeo discolor* ethanol crude extract | - | *Salmonella typhimurium* and hepatocyte cultures | Ames test and comet assay | Non-genotoxic and anti-mutagenic effects | [122] |
| *Rosa roxburghii* fruit extract | 2–50% v/v | *Salmonella typhimurium* strains (TA98, TA100 and TA102 | Ames test (metabolic activated mutagens 2-acetylaminofluorene and aflatoxin B1) | Significant anti-mutagenic effect | [123] |
| *Rubus fruticosus* leaves, *Vaccinium myrtillus* leaves, *Potentilla erecta* roots, *Geum urbanum* aerial parts and *Phaseolus vulgaris* pods | 400, 800 and 1200 µg/mL | *Allium cepa* assay | $H_2O_2$-mediated damage | All the extracts expressed high protective activity | [79] |
| *Salvia officinalis* and *Thymus vulgaris* | - | Human HepG2 cells | Comet assay: $H_2O_2$ and 2,3-dimethoxy-1,4-naphthoquinone-induced DNA damage | Antioxidant and genoprotective capacity | [67] |
| *Saraca asoca* bark extract | 50, 100 and 500 mg/kg | *Salmonella* strains and *Swiss* albino male | Metabolic activation & cyclophosphamide induced DNA damage | Antigenotoxic and anti-mutagenic property | [125] |
| *Schinus terebinthifolius* leaves methanol extracts | 16.8, 33.6, and 50.4 mg/L | *Allium cepa* and Swiss mice | Comet and micronucleus assays | Promotes cellular genome integrity by desmutagenic and bioantimutagenic activities | [87] |
| *Selaginella bryopteris* | - | - | - | Anti-carcinogenic and chemopreventive activities | [175] |
| *Solanum aculeatissimum*, *Solanum melongena* and *Solanum torvum* | 25–100%w/w | Human lymphocytes | Comet assay: $H_2O_2$-induced oxidative DNA damage | Inhibited oxidative DNA damage | [76] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Spondias mombin, Nymphea lotus* and *Luffa cylindrica* root aqueous extracts | 0.5-20 mg/mL | *Allium cepa* assay | Nitrate-induced chromosomal aberration | Chemopreventive activity through reduction of cytological aberration | [81] |
| *Stryphnodendron adstringens* hydroalcoholic extract | 0.012–3.92 mg/mL | Human keratinocytes and fibroblasts | GEMO assay: $H_2O_2$-triggered DNA fragmentation | Reduces oxidative DNA damage | [75] |
| *Terminalia arjuna* extracts | 50–200 µg/mL | PC-12 cells | Comet assay: $H_2O_2$-induced DNA damage | Decreased DNA damage | [64] |
| *Vaccinium ashei* berries lyophilized extract of | 2.6-3.2 mg/kg | Mouse hippocampus and cerebral cortex | Comet assay: $H_2O_2$-induced DNA damage | Exerts a protective effect against DNA damage | [53] |
| *Ziziphus jujuba* fruit ethanol extracts or betulinic acid | 250, 500, 1000 & 10, 20, 40 µg/mL (24 h exposure) | Liver, kidney and bone marrow cells of mice | Comet assay: methyl methanesulfonate-induced DNA damage | Inhibited DNA damage in a dose-related manner | [176] |
| **Plant and natural products** | | | | | |
| Bee-pollen or propolis | 2.5% | *Oreochromis niloticus* | Comet assay | Reduction in the frequency of CA, MN and DNA-fragmentation | [115] |
| Black liquor waste (major by-product of palm oil) | 50, 100 and 200 mg/kg | Mouse bone marrow cells | Comet assay: cyclophosphamide-induced DNA damage | Decreases MN frequency and recovered polychromatic erythrocytes (PCE)/ normochromatic erythrocytes (NME) ratio | [114] |
| Buckwheat and tartary buckwheat flour | - | Human hepatoma (HepG2) cell line | Tert-butyl hydroperoxide induced DNA damage | Both decreased DNA damage | [43] |
| Brewers' spent grain (a by-product of the brewing industry) | 2.5% v/v | U937 cells | Comet assay: $H_2O_2$-induced DNA damage | Decrease DNA damage | [65] |
| *Coffea* sp. Melanoidin-digested fractions of coffee beans | 50 µL | HT-29 cells | Alkaline comet assay | Decrease DNA oxidative damage | [177] |

| Extracts/ Preparations | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| *Coffea* sp. Spent coffee extract | 37–1000 μg/mL | Human (HeLa) cells at short (2 h) and long (24 h) exposure times | Comet assay: $H_2O_2$-induced DNA damage | Significant decreased oxidative DNA damage after 24 h exposure | [40] |
| Commercial grape-procyanidins and citrus flavonoids extract | - | *Swiss* mice | X-ray radiation (50 cGy) induced genotoxicity | Reduced the frequency of MNPE in mouse bone marrow | [178] |
| Commercial orange juice | - | Human (n = 6) lymphocytic | Alkaline comet assay: $H_2O_2$-induced DNA damage | Decreases DNA damage | [93] |
| Commercial Yunzhi extract | $10^1$–$10^5$ μg/L | Human lymphocytic | Alkaline comet assay: $H_2O_2$-induced DNA damage | Yunzhi at $10^4$ μg/L demonstrated a genoprotective effect against oxidative damage | [92] |
| Grape seed extracts | $10^{-2}$–$10^{-5}$ g/mL | Human lymphocytic | Alkaline comet assay: $H_2O_2$-induced DNA damage | Antioxidant capacity and decrease DNA damage | [60] |
| Manuka honey | 25–1000 μg/mL | Human whole blood | Comet assay: $H_2O_2$-induced DNA damage | Significant protective effect against DNA damage | [45] |
| Red wine powdered pomace seasonings | 200 μg/mL (24 h preincubation) | Colon cancerous (HT-29) cell | Comet assay: oxidative stress mediated DNA damage | Reduces oxidative DNA damage in cells | [98] |
| Roselle-Olive | 125, 250 and 500 mg/kg/day for 4 weeks | Rats | Oxidative damage | Decreases oxidative DNA damage | [96] |
| Septilin (a polyherbal drug formulation) | 125, 250 and 500 mg/kg | Bone marrow and peripheral blood cells in *Swiss* albino mice | Micronucleus assay: cyclophosphamide-indued DNA damage | No significant induction of MN, decreased clastogenic effect | [116] |
| Xiao Jian Zhong Tang (Chinese herbal preparation) | - | Human (n = 6) lymphocytic | Alkaline comet assay: $H_2O_2$-induced DNA damage | Decreases DNA damage | [94] |

ALP alkaline phosphatase, CA chromosome aberrations, CAT catalase, GPx glutathione peroxidase, GSH glutathione, GST glutathione *S*-transferase, IL interleukin, MI mitotic index, MN micronuclei, MNBC micronucleated binucleate cells, MNPE micronucleated polychromatic erythrocytes, NME normochromatic erythrocytes, PCE polychromatic erythrocytes, ROS reactive oxygen species, SWV Square wave voltammetry.

### *3.2.2. Isolated Substances*

Oxidative stress is caused by an excessive production of reactive oxygen species (ROS) and an imbalance between ROS and antioxidants, as well as a perturbation of cellular redox balance [127]. Reactive oxygen/nitrogen species (ROS/RNS) are represented by various types of radicals such as superoxide anion radical, hydroxyl, alkoxyl, and lipid peroxyl radicals, nitric oxide, and peroxynitrite that cause oxidative stress. Oxidative stress causes structural modifications and loss of functions of cellular macromolecules, including carbohydrates, lipids, proteins, and nucleic acids (e.g., DNA, RNA). Protein, including nucleoprotein damage may occur with thiol oxidation, carbonylation, side-chain oxidation, fragmentation, unfolding and misfolding, resulting in loss of activity [128].

Natural antioxidants present in food and medicinal plants, such as polyphenols, flavonoids, and carotenoids, have many important biological effects, including antioxidant, anti-inflammatory, anti-aging, anti-atherosclerosis, and anticancer effects. Effective extraction and proper use of these substances from food and medicinal plants are crucial for exploring the potential antioxidant sources, and to promote their application [129]. Table 2 presents the substances isolated from various biological sources that show genoprotective effects on experimental animals [112,130-132] or human and animal cells [54,106,133-151] and tissues [152-155], *Allium cepa* assay [156], and on other test systems [157,158]. Findings from this review suggest that substances of natural origin can act against chemical/drug-induced oxidative stress on cellular DNA such as celastrol which has been proposed as a therapeutic option to reduce cisplatin-induced nephrotoxicity [146]. Moreover, some substances such as retinoids, isolated from the roots of *Boerhaavia diffusa*, increase the level of antioxidative enzyme SOD [134], whereas naringin increases the levels of GPx and SOD in animal cells [152].

### *3.2.3. Synthetic Derivatives*

Cyclophosphamide (CP) has been recognized as one of the most widely used antineoplastic drugs, apart from being a powerful immunosuppressive agent. It is also the most frequently used drug in blood and marrow transplantation (BMT), but its adverse effects are hepatotoxicity and genotoxicity. It has been shown that CP, at relatively large concentrations, induces cytogenotoxic effects on certain types of cells, including bone marrow stem cells, liver, and intestinal epithelium of the host [159]. Alternatively, oxovanadium-L-cysteine methyl ester (1, 3, and 5 mg/kg) significantly reduced CA, MN formation, and DNA fragmentation in mouse lymphocytes, and could protect against CP-induced hepatotoxicity and genotoxicity *in vivo* [160].

On the other hand, hydrogen peroxide ($H_2O_2$) can oxidize a wide range of substrates including genetic material and causes biological damage. It can generate hydroxyl radicals ($^{\bullet}OH$) and higher oxidation states of iron, which could be toxic for normal cells [161]. Interestingly, mycosporine-2-glycine (0.1–100 μM) a natural substance used as a sunscreen, was found to have significant antioxidant activity and protect against $H_2O_2$-induced oxidative damage to DNA in human melanoma (A375 and NHSF) cells [162].

Doxorubicin (DOX) is a widely used drug in the treatment of a broad spectrum of human types of cancer. However, it causes myelosuppression and genotoxicity that may cause secondary malignancy and dose-dependent cardiotoxicity [163]. It interacts with DNA by intercalation and inhibits macromolecular biosynthesis [164]. It also stabilizes the topoisomerase II complex that can increase quinone-type free radical production, and therefore having a cytotoxic effect on cells [165]. Hajra, Patra, Basu and Bhattacharya [163] analyzed the bioactivity of indole-3-carbinol against DOX-induced toxicity in mice. They have found that indole-3-carbinol at 20 mg/kg has antioxidant and anti-inflammatory effects in *Swiss* albino mice, and they have suggested that this compound has promising chemo-protective effects against DOX-induced toxicity, therefore, they have suggested that it could be used as an adjuvant treatment in chemotherapy [163]. Table 3 presents some genoprotective synthetic derivatives.

**Table 2**. Genoprotective effects of isolated compounds

| Isolated compounds | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| BTK-8L from plant steroids | - | - | Tetrachloromethane-induced toxicity | Lowering of the death rate | [130] |
| β-Carotene | 5 mg/kg (p.o.) for 7 consecutive days | Rats | Gamma irradiation (7 Gy) exposure | Significant inhibition of fequency of micronucleus (MN) formation, the ratio of PCEs/NCEs and the mitotic index (MI) in the bone marrow cells | [136] |
| Carnosol | - | PNT2 (normal prostate) and B16F10 (melanoma) cell lines | X-ray doses (4, 6, 8 and 10 Gy) induced DNA damage | Decrease DNA damage | [142] |
| Celastrol | 50, 100 and 200 nM | NRK-52E cells | Alkaline comet assay. Cisplatin-induced nephrotoxicity | Reduced DNA damage. Improved oxidative stress markers. | [146] |
| Chlorogenic acid | 200 µM | HL-60 cells | Comet assay / 4-nitroquinoline 1-oxide | Antigenotoxic and antioxidative effect | [147] |
| Chlorogenic acid | 5 and 50 µM | HL-60 cells | Micronucleus assay | Significant genoprotective capacity | [148] |
| Citroflavan-3-ol | - | U937 cells | Comet assay: hydrogen peroxide ($H_2O_2$) and tert-butylhydroperoxide induced DNA damage | Showed protective effects against oxidative DNA damage | [54] |
| Curcumin | 100 mg/kg | Lung and livers of male *Swiss* albino mice | Benzo(a)pyrene-induced DNA damage | Significantly decreased the levels of 8-oxo-2'-deoxyguanosine content and %DNA in the comet tail in both tissues | [153] |
| Curcumin | 100 mg/kg (p.o.) | Rats | Micronucleus assay: cypermethrin-induced DNA damage | Significant reduction in MN formation and, marked reduction in DNA damage | [131] |
| Curcumin | 100 mg/kg daily for 10 weeks | Rats | Comet assay: mancozeb-induced genotoxicity | Genoprotective effect | [132] |

| Isolated compounds | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| Cynarin | 12-194 µM | Human lymphocytes | Chromosome aberrations, sister chromatid exchanges, micronucleus, and comet assays | Antigenotoxic effects rather than genotoxic effects | [150] |
| Essential oils from *Lippia* spp. | - | SOS Chromotest | UV-induced DNA damage | Reduced DNA damage | [157] |
| Epigallocatechin gallate | 0.5 and 5 µM | HL-60 cells | Micronucleus assay | Significant genoprotective capacity | [148] |
| Flavonoids from cocoa | 2 g for 6 months | Buccal epithelial cells | Comet assay | Dark chocolate significantly prevented DNA damage and improved the nucleus integrity | [144] |
| Gambogic acid | 0.01–1.0 mM | *Allium cepa* | Chromosomal aberration assay: $H_2O_2$-induced DNA damage | Antigenotoxic effect at lower concentration | [156] |
| Gallic acid | 100, 200 and 400 mg/kg | Swiss albino mice | Bone marrow and peripheral blood micronucleus assays and comet assay | Reduced the frequency of micronucleus and DNA strand breaks induced by cyclophosphamide. | [149] |
| Geraniol | 10–100 µg/mL | Human lymphocyte | *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine induced DNA damage | Reduced the frequency of chromosome aberrations and MN | [145] |
| Hyaluronic acid | 0.2% | Cultured human corneal epithelial cells | Alkaline comet assay: benzalkonium chloride-induced DNA damage | Decrease DNA damage (tail length and tail moment, and by γH2AX foci formation) and cell apoptosis | [139] |
| Morin | 5–20 µM | Pancreatic β-cells | Comet assay: $H_2O_2$- induced DNA damage | Reduced DNA damage | [143] |
| Myricetin | 25–100 µM | Primary rat hepatocytes | Ferric nitrilotriacetate induced genotoxicity | Decreased oxidative DNA damage | [135] |

| Isolated compounds | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| Naringin | 2.5 at 50 µM | DNA biosensor | Square wave voltammetry (SWV) technique | Higher antioxidant effect at concentration of up to 10 µM. No clear conclusion, an excessive naringin concentration induces DNA oxidation | [158] |
| Naringin | 20 and 40 mg/kg | Liver kidney and brain cells of Balb/C mice | - | Significantly increased in GPx and SOD, while reducing lipid peroxidation at 40 mg/kg | [152] |
| Pelargonidin chloride | 0.5 µM | HL-60 cells | Comet assay / 4-nitroquinoline 1-oxide | Antigenotoxic and antioxidative effect | [147] |
| Pelargonidin chloride | 0.05 and 0.5 µM | HL-60 cells | Micronucleus assay | Significant genoprotective capacity | [148] |
| Piperine | 20 mg | Lung and livers of male *Swiss* albino mice | Benzo(a)pyrene-induced DNA damage | Significantly decreased the levels of 8-oxo-2′-deoxyguanosine content and %DNA in the comet tail in both tissues | [153] |
| Polysaccharides from *Tussilago farfara* | 20 mg/kg (14 days) | Bone marrow cells and small intestinal epithelium in C57Bl/6 mice | Comet assay | Reduced the intensity of polychemotherapy-induced apoptosis and DNA damage | [154] |
| Quercetin | 0.01–100 µM | NCTC 2544 cells | $H_2O_2$ and $UV_C$ radiation induced genotoxicity | Genoprotective activity on mitochondrial DNA | [137] |
| Quercetin | 10-100 mg/kg body weight | Swiss mice | Gamma radiation exposure | Mitigation of radiation-induced mortality and cytogenetic damage | [151] |
| Retinoids isolated from the roots of *Boerhaavia diffusa* | - | Caco-2 cells | Comet assay: $H_2O_2$-induced DNA damage | Boeravinone G increased SOD activity and reduced DNA damage | [134] |
| Resveratrol | 10 and 100 nM | HL-60 cells | Micronucleus assay | Significant genoprotective capacity | [148] |

| Isolated compounds | Dose/Conc. (R/A) | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| Resveratrol | - | U937 cells | Comet assay: hydrogen peroxide ($H_2O_2$) and tert-butylhydroperoxide induced DNA damage | Showed protective effects against oxidative DNA damage | [54] |
| Resveratrol | 100 µM | C6 astrocyte cell line | Ammonia-induced DNA damage | Prevented DNA damage | [133] |
| Resveratrol | 10, 15, 25, 40, 75 and 100 µM | Lymphocytes | Aflatoxin $B_1$-induced DNA damage | Reduced DNA damage that leads to the formation of chromosomal aberrations (CA) and sister chromatid exchanges | [141] |
| Rutin | 10-100 mg/kg body weight | Swiss mice | Gamma radiation exposure | Mitigation of radiation-induced mortality and cytogenetic damage | [151] |
| Rosmarinic acid | 10–40 µM | Human (n = 2) lymphocytes & melanoma cells | Micronucleus assay and X-ray-induced genotoxicity | Significant genoprotective capacity | [106] |
| Thymoquinone | 1, 5 and 10 µg/mL | PC12 cells | Alkaline comet assay: ischemic insult | A dose-dependent significant decrease in DNA damage profile | [140] |
| Vitamin E and F | 50 and 100 mg/kg | Rats | Arsenic-intoxication | Significant reduction in the frequency of MN-induced apoptosis and oxidative stress | [112] |
| Zingerone | 10 µg/mL | Human lymphocytes | Cytokinesis blocked micronucleus assay: 2Gy gamma radiation induced DNA damage | Protective effect against DNA damage | [138] |

**Table 3**. Genoprotective effects of synthetic derivatives from natural products.

| Derivatives | Dose/ Concentration | Test system | Test model | Findings | References |
|---|---|---|---|---|---|
| Indole-3-carbinol | 20 mg/kg | *Swiss* albino mice | Comet assay: doxorubicin-induced genotoxic | Antioxidant, anti-inflammatory and genoprotective effects | [163] |
| Mycosporine-2-glycine | 0.1–100 µM | Human melanoma (A375 and NHSF) cell lines | Comet assay: hydrogen peroxide induced DNA damage | Protected the DNA against oxidative damage | [162] |
| Oxovanadium-L-cysteine methyl ester | 1, 3 and 5 mg/kg | Mouse lymphocytes | Comet assay: cyclophosphamide-induced DNA damage | Significant reduction of chromosomal aberrations, micronuclei formation, DNA fragmentation | [160] |

## 4. Conclusions

The data presented in this review indicate that several substances derived from natural origin can be developed as commercial products for human medicine, veterinary medicine, and for healthy food as well as for plant protection. The findings of this critical review also indicate that the pharmaceutical industry moves towards screening of synthetic chemical libraries for substances that are effective against many potential therapeutic targets, including new targets identified from the human genome sequencing project, largely to exclude natural products. Considering the high volume of natural products sold in the different countries for therapeutic purposes, it is important to know their efficacy and safety. This review analyzes a number of medicinal herbs, fungi, and marine products, as well as their derivatives which have genoprotective effects in different prokaryotic and eukaryotic test systems. Accordingly, this paper might be a source of information to researchers, especially to those who work in the field of development of drugs from natural origin.

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## References

[1] H. Turkez, M.E. Arslan and O. Ozdemir (2017). Genotoxicity testing: progress and prospects for the next decade, *Expert. Opin. Drug. Metab. Toxicol.* **13**, 1089-1098.

[2] D. Cruceriu, O. Balacescu and E. Rakosy (2018). *Calendula officinalis*: Potential roles in cancer treatment and palliative care, *Integr. Cancer Ther.* **17**, 1068-1078.

[3] E.I. Brima (2017). Toxic elements in different medicinal plants and the impact on human health, *Int. J. Environ. Res. Public Health* **14**, 1209.

[4] F.S. Poswal, G. Russell, M. Mackonochie, E. MacLennan, E.C. Adukwu and V. Rolfe (2019). Herbal teas and their health benefits: A scoping review, *Plant Foods Hum. Nutr.* **74**, 266-276.

[5] J. Zhang, D. Barałkiewicz, A. Hanć, J. Falandysz and Y. Wang (2020). Contents and health risk assessment of elements in three edible cctomycorrhizal fungi (Boletaceae) from polymetallic soils in Yunnan Province, SW China, *Biol. Trace Elem. Res.* **195**, 250-259.

[6] V. Pereira, A. Marques, I. Gaivão, A. Rego, H. Abreu, R. Pereira, M.A. Santos, S. Guilherme and M. Pacheco (2019). Marine macroalgae as a dietary source of genoprotection in gilthead seabream (*Sparus aurata*) against endogenous and exogenous challenges, *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **219**, 12-24.

[7] H.M. Sayed, D. Fouad, F.S. Ataya, N.H. Hassan and M.A. Fahmy (2012). The modifying effect of selenium and vitamins A, C, and E on the genotoxicity induced by sunset yellow in male mice, *Mutat. Res.* **744**, 145-153.

[8] W.O. Castillo, A.F. Aristizabal-Pachon, A.P. de Lima Montaldi, E.T. Sakamoto-Hojo and C.S. Takahashi (2016). Galanthamine decreases genotoxicity and cell death induced by β-amyloid peptide in SH-SY5Y cell line, *Neurotoxicology* **57**, 291-297.

[9] C.T. Che, M.S. Wong and C.W. Lam (2016). Natural products from Chinese medicines with potential benefits to bone health, *Molecules* **21**, 239.

[10] R.P. Coelho, D.L. Feksa, P.M. Oliveira, A.A. da Costa Güllich, B.C. Pilar, J. da Costa Escobar Piccoli and V. Manfredini (2018). Protective effect of the hydroalcoholic extract of *Tripodanthus acutifolius* in hypercholesterolemic Wistar rats, *Biomed. Pharmacother.* **97**, 300-309.

[11] I. Gubskiĭ Iu, E.L. Levitskiĭ, D. Kholodova Iu, A.G. Goriushko, R.G. Primak, I.E. Vistunova and L.G. Sachenko (1993). [Mechanisms of genoprotective action of a phytoecdysteroid drug(BTK-8L) in chromatin damage by tetrachloromethane], *Ukr. Biokhim. Zh. (1978)* **65**, 75-83.

[12] V.N. Chabannyĭ, E.L. Levitskiĭ, I. Gubskiĭ Iu, D. Kholodova Iu, I.E. Vistunova and M.I. Budmaska (1994). [Genoprotective effect of drugs based on ecdysteroids in poisoning of rats with tetrachloromethane and chlorophos], *Ukr. Biokhim. Zh. (1978)* **66**, 67-77.

[13] G. Statti, M. Marrelli, F. Conforti, A. Spagnoletti, M. Tacchini, C. Fimognari, E. Brognara, R. Gambari, G. Sacchetti and A. Guerrini (2015). Inhibition of cancer cell proliferation and antiradical effects of decoction, hydroalcoholic extract, and principal constituents of *Hemidesmus indicus* R. Br, *Phytother. Res.* **29**, 857-863.

[14] D.W. Al-Dualimi, A. Shah Abdul Majid, S.F.F. Al-Shimary, A.A. Al-Saadi, R. Al Zarzour, M. Asif, C. Ein Oon and A.M.S. Abdul Majid (2018). 50% Ethanol extract of *Orthosiphon stamineus* modulates genotoxicity and clastogenicity induced by mitomycin C, *Drug. Chem. Toxicol.* **41**, 82-88.

[15] S. Kalthoff, U. Ehmer, N. Freiberg, M.P. Manns and C.P. Strassburg (2010). Coffee induces expression of glucuronosyltransferases by the aryl hydrocarbon receptor and Nrf2 in liver and stomach, *Gastroenterology* **139**, 1699-1710, 1710.e1691-1692.

[16] L. Goya, S. Ramos, M.A. Martín and F.J. Morales (2015). Chapter 102: Cytoprotective effect of coffee melanoidins, In: Coffee in health and disease prevention, 2015; pp. 921-929.

[17] R.T. Abib, A. Quincozes-Santos, C. Zanotto, F. Zeidán-Chuliá, P.S. Lunardi, C.A. Gonçalves and C. Gottfried (2010). Genoprotective effects of the green tea-derived polyphenol/epicatechin gallate in C6 astroglial cells, *J. Med. Food* **13**, 1111-1115.

[18] K.C. Han, W.C. Wong and I.F. Benzie (2011). Genoprotective effects of green tea (*Camellia sinensis*) in human subjects: Results of a controlled supplementation trial, *Br. J. Nutr.* **105**, 171-179.

[19] S.W. Choi, V.T. Yeung, A.R. Collins and I.F. Benzie (2015). Redox-linked effects of green tea on DNA damage and repair, and influence of microsatellite polymorphism in HMOX-1: Results of a human intervention trial, *Mutagenesis* **30**, 129-137.

[20] J.W. Yuen and M.D. Gohel (2008). The dual roles of *Ganoderma* antioxidants on urothelial cell DNA under carcinogenic attack, *J. Ethnopharmacol.* **118**, 324-330.

[21] S. Ponnala, K.P. Rao, J.R. Chaudhury, J. Ahmed, B. Rama Rao, S. Kanjilal, Q. Hasan and U.N. Das (2009). Effect of polyunsaturated fatty acids on diphenyl hydantoin-induced genetic damage in vitro and in vivo, *Prostaglandins Leukot. Essent. Fatty Acids* **80**, 43-50.

[22] A. Mbaveng, Q. Zhao and V. Kuete (2014). Harmful and protective effects of phenolic compounds from African medicinal plants, In: Toxicological Survey of African Medicinal Plants, ed: V. Kuete, Elsevier, Amsterdam, Netherlands, pp. 677-710.

[23] A.C. Aprotosoaie, V.S. Luca, A. Trifan and A. Miron (2019). Chapter 7-Antigenotoxic potential of some dietary non-phenolic phytochemicals, *Stud. Nat. Prod. Chem.* **60**, 223-297.

[24] A.C. Aprotosoaie, C.T. Mihai, G. Vochita, P. Rotinberg, A. Trifan, S.V. Luca, T. Petreus, E. Gille and A. Miron (2016). Antigenotoxic and antioxidant activities of a polyphenolic extract from European *Dracocephalum moldavica* L, *Ind. Crops. Prod.* **79**, 248-257.

[25] Y.T. Szeto, A.R. Collins and I.F. Benzie (2002). Effects of dietary antioxidants on DNA damage in lysed cells using a modified comet assay procedure, *Mutat. Res.* **500**, 31-38.

[26] A. Quincozes-Santos, A.C. Andreazza, P. Nardin, C. Funchal, C.A. Gonçalves and C. Gottfried (2007). Resveratrol attenuates oxidative-induced DNA damage in C6 Glioma cells, *Neurotoxicology* **28**, 886-891.

[27] W. Thilakarathna and H.P.V. Rupasinghe (2019). Microbial metabolites of proanthocyanidins reduce chemical carcinogen-induced DNA damage in human lung epithelial and fetal hepatic cells in vitro, *Food Chem. Toxicol.* **125**, 479-493.

[28] S. Ling, Y. Wu, J. Zheng, J. Linden and J. Holoshitz (2004). Genoprotective pathways. II. Attenuation of oxidative DNA damage by isopentenyl diphosphate, *Mutat. Res.* **554**, 33-43.

[29] J.A. Izquierdo-Vega, J.A. Morales-González, M. SánchezGutiérrez, G. Betanzos-Cabrera, S.M. Sosa-Delgado, M.T. Sumaya-Martínez, Á. Morales-González, R. Paniagua-Pérez, E. Madrigal-Bujaidar and E. Madrigal-Santillán (2017). Evidence of some natural products with antigenotoxic effects. Part 1: Fruits and polysaccharides, *Nutrients* **9**, 102.

[30] D. López-Romero, J.A. Izquierdo-Vega, J.A. Morales-González, E. Madrigal-Bujaidar, G. Chamorro-Cevallos, M. Sánchez-Gutiérrez, G. Betanzos-Cabrera, I. Alvarez-Gonzalez, Á. Morales-González and E. Madrigal-Santillán (2018). Evidence of some natural products with antigenotoxic effects. Part 2: Plants, vegetables, and natural resin, *Nutrients* **10**, 1954.

[31] A.R. Collins (2004). The comet assay for DNA damage and repair: principles, applications, and limitations, *Mol. Biotechnol.* **26**, 249-261.

[32] N.P. Singh (2016). The comet assay: Reflections on its development, evolution and applications, *Mutat. Res. Rev. Mutat. Res.* **767**, 23-30.

[33] G. Koppen, A. Azqueta, B. Pourrut, G. Brunborg, A.R. Collins and S.A.S. Langie (2017). The next three decades of the comet assay: A report of the 11th International Comet Assay Workshop, *Mutagenesis* **32**, 397-408.

[34] L. Koklesova, A. Liskova, M. Samec, T. Qaradakhi, A. Zulli, K. Smejkal, K. Kajo, J. Jakubikova, P. Behzadi, M. Pec, P. Zubor, K. Biringer, T.K. Kwon, D. Büsselberg, G.R. Sarria, F.A. Giordano, O. Golubnitschaja and P. Kubatka (2020). Genoprotective activities of plant natural substances in cancer and chemopreventive strategies in the context of 3P medicine, *EPMA J.* **11**, 261-287.

[35] Q. Wu, X. Wang, E. Nepovimova, Y. Wang, H. Yang, L. Li, X. Zhang and K. Kuca (2017). Antioxidant agents against trichothecenes: New hints for oxidative stress treatment, *Oncotarget.* **8**, 110708-110726.

[36] K. Shingnaisui, T. Dey, P. Manna and J. Kalita (2018). Therapeutic potentials of *Houttuynia cordata* Thunb. against inflammation and oxidative stress: A review, *J. Ethnopharmacol.* **220**, 35-43.

[37] E.T. Bacolod, S. Uno, S.S. Villamor and J. Koyama (2017). Oxidative stress and genotoxicity biomarker responses in tilapia (*Oreochromis niloticus*) exposed to environmental concentration of 1-nitropyrene, *Mar. Pollut. Bull.* **124**, 786-791.

[38] D. Erba, P. Riso, A. Colombo and G. Testolin (1999). Supplementation of Jurkat T cells with green tea extract decreases oxidative damage due to iron treatment, *J. Nutr.* **129**, 2130-2134.

[39] D. Erba, P. Riso, P. Foti, F. Frigerio, F. Criscuoli and G. Testolin (2003). Black tea extract supplementation decreases oxidative damage in Jurkat T cells, *Arch. Biochem. Biophys.* **416**, 196-201.

[40] J. Bravo, L. Arbillaga, M.P. de Peña and C. Cid (2013). Antioxidant and genoprotective effects of spent coffee extracts in human cells, *Food Chem. Toxicol.* **60**, 397-403.

[41] C.K. Ho, S.W. Choi, P.M. Siu and I.F. Benzie (2014). Effects of single dose and regular intake of green tea (*Camellia sinensis*) on DNA damage, DNA repair, and heme oxygenase-1 expression in a randomized controlled human supplementation study, *Mol. Nutr. Food Res.* **58**, 1379-1383.

[42] C.K. Ho, C. Siu-wai, P.M. Siu and I.F. Benzie (2013). Genoprotection and genotoxicity of green tea (*Camellia sinensis*): Are they two sides of the same redox coin?, *Redox Rep.* **18**, 150-154.

[43] M. Vogrinčič, I. Kreft, M. Filipič and B. Zegura (2013). Antigenotoxic effect of Tartary (*Fagopyrum tataricum*) and common (*Fagopyrum esculentum*) buckwheat flour, *J. Med. Food.* **16**, 944-952.

[44] M. Ježovičová, K. Koňariková, Z. Ďuračková, J. Keresteš, G. Králik and I. Žitňanová (2016). Protective effects of black tea extract against oxidative DNA damage in human lymphocytes, *Mol. Med. Rep.* **13**, 1839-1844.

[45] L. Živković, V. Bajić, D. Dekanski, A. Čabarkapa-Pirković, F. Giampieri, M. Gasparrini, L. Mazzoni and B.S. Potparević (2018). Manuka honey attenuates oxidative damage induced by $H_2O_2$ in human whole blood in vitro, *Food Chem. Toxicol.* **119**, 61-65.

[46] J.C. Ribeiro, L.M. Antunes, A.F. Aissa, J.D. Darin, V.V. De Rosso, A.Z. Mercadante and L. Bianchi Mde (2010). Evaluation of the genotoxic and antigenotoxic effects after acute and subacute treatments with açai pulp (*Euterpe oleracea* Mart.) on mice using the erythrocytes micronucleus test and the comet assay, *Mutat. Res.* **695**, 22-28.

[47] J.A. Morales-González, E. Madrigal-Bujaidar, M. Sánchez-Gutiérrez, J.A. Izquierdo-Vega, M.D.C. Valadez-Vega, I. Álvarez-González, Á. Morales-González and E. Madrigal-Santillán (2019). Garlic (*Allium sativum* L.): A brief review of its antigenotoxic effects, *Foods* **8**, 343.

[48] M. Kalemba-Drożdż, I. Kwiecień, A. Szewczyk, A. Cierniak and A. Grzywacz-Kisielewska (2020). Fermented vinegars from apple peels, raspberries, rosehips, lavender, mint, and rose petals: The composition, antioxidant power, and genoprotective abilities in comparison to acetic macerates, decoctions, and tinctures, *Antioxidants* **9**, 1121.

[49] I.-C. Jang, E.-K. Jo, M.-S. Bae, H.-J. Lee, G.-I. Jeon, E. Park, H.-G. Yuk, G.-H. Ahn and S.-C. Lee (2010). Antioxidant and antigenotoxic activities of different parts of persimmon (*Diospyros kaki* cv. Fuyu) fruit, *J. Med. Plants Res.* **4**, 155-160.

[50] M.V. Dassprakash, R. Arun, S.K. Abraham and K. Premkumar (2012). In vitro and in vivo evaluation of antioxidant and antigenotoxic potential of *Punica granatum* leaf extract, *Pharm. Biol.* **50**, 1523-1530.

[51] T.M. de Kok, P. de Waard, L.C. Wilms and S.G. van Breda (2010). Antioxidative and antigenotoxic properties of vegetables and dietary phytochemicals: the value of genomics biomarkers in molecular epidemiology, *Mol. Nutr. Food Res.* **54**, 208-217.

[52] G.D. Zasukhina, I.M. Vasil'eva, E.S. Mikhal'chik, A.D. Durnev, S.P. Gromov, O.A. Fedorova and M.V. Alfimov (2003). Antimutagenic and antioxidant activities of crown compounds in comparison with the effects of garlic extract, *Bull. Exp. Biol. Med.* **135**, 261-264.

[53] D. Barros, O.B. Amaral, I. Izquierdo, L. Geracitano, M. do Carmo Bassols Raseira, A.T. Henriques and M.R. Ramirez (2006). Behavioral and genoprotective effects of *Vaccinium* berries intake in mice, *Pharmacol. Biochem. Behav.* **84**, 229-234.

[54] N.M. O'Brien, R. Carpenter, Y.C. O'Callaghan, M.N. O'Grady and J.P. Kerry (2006). Modulatory effects of resveratrol, citroflavan-3-ol, and plant-derived extracts on oxidative stress in U937 cells, *J. Med. Food.* **9**, 187-195.

[55] S.A. Aherne, J.P. Kerry and N.M. O'Brien (2007). Effects of plant extracts on antioxidant status and oxidant-induced stress in Caco-2 cells, *Br. J. Nutr.* **97**, 321-328.

[56] V. Vijayan and A. Helen (2007). Protective activity of *Bacopa monniera* Linn. on nicotine-induced toxicity in mice, *Phytother. Res.* **21**, 378-381.

[57] M. Phelan, S.A. Aherne, A. Wong and N.M. O'Brien (2009). Bioactive properties of wood knot extracts on cultured human cells, *J. Med. Food* **12**, 1245-1251.

[58] Y.T. Szeto, P.C. Lei, K.L. Ngai, A.T. Yiu, C.S. Chan, E.W. Kok and C.W. Leong (2009). An in vitro study of the antioxidant activities and effect on human DNA of the Chinese herbal decoction 'Liu Wei Di Huang', *Int. J. Food Sci. Nutr.* **60**, 662-667.

[59] Y.T. Szeto, J.W. Wong, S.C. Wong, S.C. Pak and I.F. Benzie (2011). DNA protective effect of ginseng and the antagonistic effect of Chinese turnip: A preliminary study, *Plant Foods Hum. Nutr.* **66**, 97-100.

[60] Y.T. Szeto, K.Y. Lee, W. Kalle and S.C. Pak (2013). Protective effect of grape seed extracts on human lymphocytes: A preliminary study, *Appl. Physiol. Nutr. Metab.* **38**, 275-279.

[61] V. Rajkumar, G. Guha and R.A. Kumar (2010). Therapeutic potential of *Acalypha fruticosa*, *Food Chem. Toxicol.* **48**, 1709-1713.

[62] K.M. Ramkumar, L. Sankar, C. Manjula, K. Krishnamurthi, S.S. Devi, T. Chakrabarti, K. Kalaiselvi, M. Palanivel and P. Rajaguru (2010). Antigenotoxic potential of *Gymnema montanum* leaves on DNA damage in human peripheral blood lymphocytes and HL-60 cell line, *Environ. Mol. Mutagen.* **51**, 285-293.

[63] M. Kumar, M. Chandel, N. Sharma, S. Kumar and S. Kaur (2012). Efficacy of golden rain tree against free radicals and $H_2O_2$-induced damage to pUC18/calf thymus DNA, *Asian Pac. J. Trop. Biomed.* **2**, S781-S787.

[64] G. Phani Kumar, K. Navya, E.M. Ramya, M. Venkataramana, T. Anand and K.R. Anilakumar (2013). DNA damage protecting and free radical scavenging properties of *Terminalia arjuna* bark in PC-12 cells and plasmid DNA, *Free Rad. Antiox.* **3**, 35-39.

[65] A.L. McCarthy, Y.C. O'Callaghan, A. Connolly, C.O. Piggott, R.J. Fitzgerald and N.M. O'Brien (2012). Phenolic extracts of brewers' spent grain (BSG) as functional ingredients - assessment of their DNA protective effect against oxidant-induced DNA single strand breaks in U937 cells, *Food Chem.* **134**, 641-646.

[66] L.S. Bittencourt, D.C. Machado, M.M. Machado, G.F. Dos Santos, T.D. Algarve, D.R. Marinowic, E.E. Ribeiro, F.A. Soares, F. Barbisan, M.L. Athayde and I.B. Cruz (2013). The protective effects of guaraná extract (*Paullinia cupana*) on fibroblast NIH-3T3 cells exposed to sodium nitroprusside, *Food Chem. Toxicol.* **53**, 119-125.

[67] K. Kozics, V. Klusová, A. Srančíková, P. Mučaji, D. Slameňová, L. Hunáková, B. Kusznierewicz and E. Horváthová (2013). Effects of *Salvia officinalis* and *Thymus vulgaris* on oxidant-induced DNA damage and antioxidant status in HepG2 cells, *Food Chem.* **141**, 2198-2206.

[68] M. Shokrzadeh, A. Chabra, F. Naghshvar and A. Ahmadi (2013). The mitigating effect of *Citrullus colocynthis* (L.) fruit extract against genotoxicity induced by cyclophosphamide in mice bone marrow cells, *Sci. World J.* **2013**, 980480.

[69] Z. Abdul Hamid, W.H. Lin Lin, B.J. Abdalla, O. Bee Yuen, E.S. Latif, J. Mohamed, N.F. Rajab, C. Paik Wah, M.K. Wak Harto and S.B. Budin (2014). The role of *Hibiscus sabdariffa* L. (Roselle) in maintenance of ex vivo murine bone marrow-derived hematopoietic stem cells, *Sci. World J.* **2014**, 258192.

[70] D. Iqbal, M.S. Khan, A. Khan, M.S. Khan, S. Ahmad, A.K. Srivastava and P. Bagga (2014). In vitro screening for β-hydroxy-β-methylglutaryl-CoA reductase inhibitory and antioxidant activity of sequentially extracted fractions of *Ficus palmata* Forsk, *Biomed. Res. Int.* **2014**, 762620.

[71] I. Rajan, R. Rabindran, P.R. Jayasree and P.R. Kumar (2014). Antioxidant potential and oxidative DNA damage preventive activity of unexplored endemic species of *Curcuma*, *Indian J. Exp. Biol.* **52**, 133-138.

[72] A. Sassi, I. Bouhlel, N. Mustapha, I. Mokdad-Bzeouich, F. Chaabane, K. Ghedira and L. Chekir-Ghedira (2016). Assessment in vitro of the genotoxicity, antigenotoxicity and antioxidant of *Ceratonia siliqua* L. extracts in murine leukaemia cells L1210 by comet assay, *Regul. Toxicol. Pharmacol.* **77**, 117-124.

[73] M. Yasir, B. Sultana, P.S. Nigam and R. Owusu-Apenten (2016). Antioxidant and genoprotective activity of selected Cucurbitaceae seed extracts and LC-ESIMS/MS identification of phenolic components, *Food Chem.* **199**, 307-313.

[74] A. Rouamba, M. Compaoré, M. Ouédraogo and M. Kiendrebeogo (2018). Human lymphocyte-protective effects of an ethanol extract from *Detarium microcarpum* Guill. and Perr. (Caesalpiniaceae) fruit pulp, *Antioxidants* **7**, 104.

[75] N.L. Pellenz, F. Barbisan, V.F. Azzolin, T. Duarte, A. Bolignon, M.H. Mastella, C.F. Teixeira, E.E. Ribeiro, I.B.M. da Cruz and M. Duarte (2018). Analysis of in vitro cyto- and genotoxicity of barbatimão extract on human keratinocytes and fibroblasts, *Biomed. Res. Int.* **2018**, 1942451.

[76] M. Sukprasansap, P. Sridonpai and P.P. Phiboonchaiyanan (2019). Eggplant fruits protect against DNA damage and mutations, *Mutat. Res.* **813**, 39-45.

[77] G.I. Peredo Pozos, M.A. Ruiz-López, J.F. Zamora Nátera, C. Álvarez Moya, L. Barrientos Ramírez, M. Reynoso Silva, R. Rodríguez Macías, P.M. García-López, R. González Cruz, E. Salcedo Pérez and J.J. Vargas Radillo (2020). Antioxidant capacity and antigenotoxic effect of *Hibiscus sabdariffa* L. extracts obtained with ultrasound-assisted extraction process, *Appl. Sci.* **10**, 560.

[78] H. Meziti, H. Bouriche, S. Kada, I. Demirtas, M. Kizil, A. Senator and G. Garrido (2019). Phytochemical analysis, and antioxidant, anti-hemolytic and genoprotective effects of *Quercus ilex* L. and *Pinus halepensis* Mill. methanolic extracts, *J. Pharm. Pharmacog. Res.* **7**, 260-272.

[79] V. Madić, Z. Stojanović-Radić, M. Jušković, D. Jugović, A. Žabar Popović and P. Vasiljević (2019). Genotoxic and antigenotoxic potential of herbal mixture and five medicinal plants used in ethnopharmacology, *S. Afr. J. Bot.* **125**, 290-297.

[80] G. Bouguellid, C. Russo, M. Lavorgna, C. Piscitelli, K. Ayouni, E. Wilson, H.K. Kim, R. Verpoorte, Y.H. Choi, D. Kilani-Atmani, D. Atmani and M. Isidori (2020). Antimutagenic, antigenotoxic and antiproliferative activities of *Fraxinus angustifolia* Vahl. leaves and stem bark extracts and their phytochemical composition, *PLoS One* **15**, e0230690.

[81] I.T. Oyeyemi and A.A. Bakare (2013). Genotoxic and anti-genotoxic effect of aqueous extracts of *Spondias mombin* L., *Nymphea lotus* L. and *Luffa cylindrica* L. on *Allium cepa* root tip cells, *Caryologia* **66**, 360-367.

[82] P. Kaur, S. Kaur, N. Kumar, B. Singh and S. Kumar (2009). Evaluation of antigenotoxic activity of isoliquiritin apioside from *Glycyrrhiza glabra* L, *Toxicol. In Vitro* **23**, 680-686.

[83] P. Kaur, W. Amandeep, K. Subodh and S. Kaur (2009). Antigenotoxic activity of polyphenolic rich extracts from *Aegle marmelos* (L.) Correa in human blood lymphocytes and *E. coli* PQ 37, *Rec. Nat. Prod.* **3**, 68-75.

[84] K. Arunachalam, S. Subhashini and K.A. Sathesh (2012). Wound healing and antigenotoxic activities of *Aegle marmelos* with relation to its antioxidant properties, *J. Pharm. Res.* **5**, 1492-1502.

[85] S. Cvetković, S. Todorović, B. Nastasijević, D. Mitić-Ćulafić, S. Đukanović, J. Knežević-Vukčević and B. Nikolić (2020). Assessment of genoprotective effects of *Gentiana lutea* extracts prepared from plants grown in field and in vitro, *Ind. Crops Prod.* **154**, 112690.

[86] N.C. de Carvalho, M.J. Corrêa-Angeloni, D.D. Leffa, J. Moreira, V. Nicolau, P. de Aguiar Amaral, A.E. Rossatto and V.M. de Andrade (2011). Evaluation of the genotoxic and antigenotoxic potential of *Melissa officinalis* in mice, *Genet. Mol. Biol.* **34**, 290-297.

[87] L.E. Fedel-Miyasato, A.S. Formagio, S.A. Auharek, C.A. Kassuya, S.D. Navarro, A.L. Cunha-Laura, A.C. Monreal, M.C. Vieira and R.J. Oliveira (2014). Antigenotoxic and antimutagenic effects of *Schinus terebinthifolius* Raddi in *Allium cepa* and Swiss mice: A comparative study, *Genet. Mol. Res.* **13**, 3411-3425.

[88] R. Figat, A. Śliwińska, A. Stochmal, A. Soluch, M. Sobczak, A. Zgadzaj, K. Sykłowska-Baranek and A. Pietrosiuk (2020). Antigenotoxic, anti-photogenotoxic, and antioxidant properties of *Polyscias filicifolia* shoots cultivated in vitro, *Molecules* **25**, 1090.

[89] B. Singh, P. Sharma, A. Kumar, P. Chadha, R. Kaur and A. Kaur (2016). Antioxidant and in vivo genoprotective effects of phenolic compounds identified from an endophytic *Cladosporium velox* and their relationship with its host plant *Tinospora cordifolia*, *J. Ethnopharmacol.* **194**, 450-456.

[90] L. Živković, V. Bajić, M. Bruić, S. Borozan, K. Popić, D. Topalović, J. Santibanez and B. Spremo-Potparević (2019). Antigenotoxic and antioxidant potential of medicinal mushrooms (Immune Assist) against DNA damage induced by free radicals-an in vitro study, *Mutat. Res.* **845**, 403078.

[91] Y.L. Shi, I.F. Benzie and J.A. Buswell (2002). Role of tyrosinase in the genoprotective effect of the edible mushroom, *Agaricus bisporus*, *Life Sci.* **70**, 1595-1608.

[92] Y.T. Szeto, P.C. Lau, W. Kalle and S.C. Pak (2013). Direct human DNA protection by *Coriolus versicolor* (Yunzhi) extract, *Pharm. Biol.* **51**, 851-855.

[93] Y.T. Szeto, T.L. To, S.C. Pak and W. Kalle (2013). A study of DNA protective effect of orange juice supplementation, *Appl. Physiol. Nutr. Metab.* **38**, 533-536.

[94] Y.T. Szeto, N.F. Cheng, S.C. Pak and W. Kalle (2013). Genoprotective effect of the Chinese herbal decoction xiao jian zhong tang, *Nat. Prod. Commun.* **8**, 389-392.

[95] J. Cilerdzic, M. Stajic, L. Zivkovic, J. Vukojevic, V. Bajic and B. Spremo-Potparevic (2016). Genoprotective capacity of alternatively cultivated lingzhi or reishi medicinal mushroom, *Ganoderma lucidum* (Agaricomycetes), basidiocarps, *Int. J. Med. Mushrooms* **18**, 1061-1069.

[96] R.F. Abdel-Rahman, A.F. Hessin, M. Abdelbaset, H.A. Ogaly, R.M. Abd-Elsalam and S.M. Hassan (2017). Antihypertensive effects of roselle-olive combination in L-NAME-induced hypertensive rats, *Oxid. Med. Cell. Longev.* **2017**, 9460653.

[97] H. Chahdoura, S. El Bok, T. Refifa, K. Adouni, F. Khemiss, H. Mosbah, M. Ben-Attia, G. Flamini and L. Achour (2017). Activity of anti-inflammatory, analgesic and antigenotoxic of the aqueous flower extracts of *Opuntia microdasys* Lem.Pfeiff, *J. Pharm. Pharmacol.* **69**, 1056-1063.

[98] R. Del Pino-García, M.D. Rivero-Pérez, M.L. González-SanJosé, M. Ortega-Heras, J. García Lomillo and P. Muñiz (2017). Chemopreventive potential of powdered red wine pomace seasonings against colorectal cancer in HT-29 Cells, *J. Agric. Food Chem.* **65**, 66-73.

[99] A. Knežević, M. Stajić, L. Živković, I. Milovanović, B. Spremo-Potparević and J. Vukojević (2017). Antifungal, antioxidative, and genoprotective properties of extracts from the blushing bracket mushroom, *Daedaleopsis confragosa* (Agaricomycetes), *Int. J. Med. Mushrooms* **19**, 509-520.

[100] R. Aliyazicioglu, S. Demir, M. Badem, S. Sener, N. Korkmaz, E. Ayazoglu demir, U. Özgen, Ş. Alpay Karaoğlu and Y. Aliyazicioglu (2017). Antioxidant, antigenotoxic, antimicrobial activities and phytochemical analysis of *Dianthus carmelitarum*, *Rec. Nat. Prod.* **11**, 270-284.

[101] S. Kumari, R. Elancheran and R. Devi (2018). Phytochemical screening, antioxidant, antityrosinase, and antigenotoxic potential of *Amaranthus viridis* extract, *Indian J. Pharmacol.* **50**, 130-138.

[102] M. Ligaj, J. Kobus-Cisowska, O. Szczepaniak, P. Szulc, D. Kikut-Ligaj, A. Mikołajczak-Ratajczak, P. Bykowski, D. Szymanowska, M. Przeor, K. Polewski and M. Jarzębski (2021). Electrochemical screening of genoprotective and antioxidative effectiveness of *Origanum vulgare* L. and its functionality in the prevention of neurodegenerative disorders, *Talanta* **223**, 121749.

[103] S. Kilani-Jaziri, W. Bhouri, I. Skandrani, I. Limem, L. Chekir-Ghedira and K. Ghedira (2011). Phytochemical, antimicrobial, antioxidant and antigenotoxic potentials of *Cyperus rotundus* extracts, *S. Afr. J. Bot.* **77**, 767-776.

[104] M. Cavinato, B. Waltenberger, G. Baraldo, C.V.C. Grade, H. Stuppner and P. Jansen-Dürr (2017). Plant extracts and natural compounds used against UVB-induced photoaging, *Biogerontology* **18**, 499-516.

[105] R.A. Agabeĭli, T.E. Kasimova and U.K. Alekperov (2004). [Antimutagenic activity of plant extracts from *Armoracia rusticana*, *Ficus carica* and *Zea mays* and peroxidase in eukaryotic cells], *Tsitol. Genet.* **38**, 40-45.

[106] M. Alcaraz, M. Alcaraz-Saura, D.G. Achel, A. Olivares, J.A. López-Morata and J. Castillo (2014). Radiosensitizing effect of rosmarinic acid in metastatic melanoma B16F10 cells, *Anticancer Res.* **34**, 1913-1921.

[107] Y.T. Szeto, Y.S. Sin, S.C. Pak and W. Kalle (2015). American ginseng tea protects cellular DNA within 2 h from consumption: Results of a pilot study in healthy human volunteers, *Int. J. Food Sci. Nutr.* **66**, 815-818.

[108] M. Fenech, M. Kirsch-Volders, A.T. Natarajan, J. Surralles, J.W. Crott, J. Parry, H. Norppa, D.A. Eastmond, J.D. Tucker and P. Thomas (2011). Molecular mechanisms of micronucleus, nucleoplasmic bridge and nuclear bud formation in mammalian and human cells, *Mutagenesis* **26**, 125-132.

[109] M. Benvindo-Souza, R.E. Borges, S.M. Pacheco and L.R.S. Santos (2019). Genotoxicological analyses of insectivorous bats (Mammalia: Chiroptera) in central Brazil: The oral epithelium as an indicator of environmental quality, *Environ. Pollut.* **245**, 504-509.

[110] H. Turkez, E. Aydin and A. Aslan (2014). Role of aqueous *Bryoria capillaris* (Ach.) extract as a genoprotective agent on imazalil-induced genotoxicity in vitro, *Toxicol. Ind. Health* **30**, 33-39.

[111] E. Habibi, M. Shokrzadeh, A. Ahmadi, A. Chabra, F. Naghshvar and R. Keshavarz-Maleki (2015). Genoprotective effects of *Origanum vulgare* ethanolic extract against cyclophosphamide-induced genotoxicity in mouse bone marrow cells, *Pharm. Biol.* **53**, 92-97.

[112] A.A. Oyagbemi, T.O. Omobowale, O.E. Ola-Davies, O.A. Adejumobi, E.R. Asenuga, F.K. Adeniji, A.A. Adedapo and M.A. Yakubu (2018). Protective effect of *Azadirachta indica* and vitamin E against arsenic acid-induced genotoxicity and apoptosis in rats, *J. Diet. Suppl.* **15**, 251-268.

[113] M.A. Hashem, W.A.M. Mohamed and E.S.M. Attia (2018). Assessment of protective potential of *Nigella sativa* oil against carbendazim- and/or mancozeb-induced hematotoxicity, hepatotoxicity, and genotoxicity, *Environ. Sci. Pollut. Res. Int.* **25**, 1270-1282.

[114] P. Naik, H.D. Rozman and R. Bhat (2013). Genoprotective effects of lignin isolated from oil palm black liquor waste, *Environ. Toxicol. Pharmacol.* **36**, 135-141.
[115] M.M. Kandiel, A.M. El-Asely, H.A. Radwan and A.A. Abbass (2014). Modulation of genotoxicity and endocrine disruptive effects of malathion by dietary honeybee pollen and propolis in Nile tilapia (*Oreochromis niloticus*), *J. Adv. Res.* **5**, 671-684.
[116] S. Shruthi and K.K. Vijayalaxmi (2016). Antigenotoxic effects of a polyherbal drug septilin against the genotoxicity of cyclophosphamide in mice, *Toxicol. Rep.* **3**, 563-571.
[117] L. Sagi-Dain and S. Sagi (2015). Chromosomal aberrations in idiopathic polyhydramnios: A systematic review and meta-analysis, *Eur. J. Med. Genet.* **58**, 409-415.
[118] R. Ananthi, N. Chandra, S.T. Santhiya and A. Ramesh (2010). Genotoxic and antigenotoxic effects of *Hemidesmus indicus* R. Br. root extract in cultured lymphocytes, *J. Ethnopharmacol.* **127**, 558-560.
[119] H. Türkez and B. Toğar (2011). Olive (*Olea europaea* L.) leaf extract counteracts genotoxicity and oxidative stress of permethrin in human lymphocytes, *J. Toxicol. Sci.* **36**, 531-537.
[120] S. Sharma, S. Sharma and A.P. Vig (2018). Antigenotoxic potential of plant leaf extracts of *Parkinsonia aculeata* L. using *Allium cepa* assay, *Plant Physiol. Biochem.* **130**, 314-323.
[121] S. Sharma, S.M. Javadekar, M. Pandey, M. Srivastava, R. Kumari and S.C. Raghavan (2015). Homology and enzymatic requirements of microhomology-dependent alternative end joining, *Cell Death Dis.* **6**, e1697.
[122] M. González-Avila, M. Arriaga-Alba, M. de la Garza, M. del Carmen Hernández Pretelín, M.A. Domínguez-Ortíz, S. Fattel-Fazenda and S. Villa-Treviño (2003). Antigenotoxic, antimutagenic and ROS scavenging activities of a *Rhoeo discolor* ethanolic crude extract, *Toxicol. In Vitro* **17**, 77-83.
[123] F.H. van der Westhuizen, C.S. van Rensburg, G.S. Rautenbach, J.L. Marnewick, T. Loots du, C. Huysamen, R. Louw, P.J. Pretorius and E. Erasmus (2008). In vitro antioxidant, antimutagenic and genoprotective activity of *Rosa roxburghii* fruit extract, *Phytother. Res.* **22**, 376-383.
[124] R.A. Agabeĭli and G.G. Mirzazade (2011). [Genoprotective activities of the oils from leaves and fruits of *Fagus orientalis* Lipsky], *Tsitol. Genet.* **45**, 23-28.
[125] D. Nag, M. Ghosh and A. Mukherjee (2015). Antimutagenic and genoprotective effects of *Saraca asoca* bark extract, *Toxicol. Ind. Health* **31**, 696-703.
[126] I. Fierascu, C. Ungureanu, S.M. Avramescu, C. Cimpeanu, M.I. Georgescu, R.C. Fierascu, A. Ortan, A.N. Sutan, V. Anuta, A. Zanfirescu, C.E. Dinu-Pirvu and B.S. Velescu (2018). Genoprotective, antioxidant, antifungal and anti-inflammatory evaluation of hydroalcoholic extract of wild-growing *Juniperus communis* L. (Cupressaceae) native to Romanian southern sub-Carpathian hills, *BMC Complement. Altern. Med.* **18**, 3.
[127] G. Scutiero, P. Iannone, G. Bernardi, G. Bonaccorsi, S. Spadaro, C.A. Volta, P. Greco and L. Nappi (2017). Oxidative stress and endometriosis: A systematic review of the literature, *Oxid. Med. Cell. Longev.* **2017**, 7265238.
[128] A.M. Pisoschi and A. Pop (2015). The role of antioxidants in the chemistry of oxidative stress: A review, *Eur. J. Med. Chem.* **97**, 55-74.
[129] D.P. Xu, Y. Li, X. Meng, T. Zhou, Y. Zhou, J. Zheng, J.J. Zhang and H.B. Li (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources, *Int. J. Mol. Sci.* **18**, 96.
[130] E.L. Levitskiĭ, D. Kholodova Iu, I. Gubskiĭ Iu, A.G. Goriushko, R.G. Primak, I.E. Vistunova and L.G. Sachenko (1993). [Mechanisms of the genoprotective action of a phytoecdysteroid drug (BTK-8L) in chromatin damage by chlorofos], *Ukr. Biokhim. Zh. (1978)* **65**, 84-91.
[131] P. Sankar, A.G. Telang and A. Manimaran (2010). Curcumin protects against cypermethrin-induced genotoxicity in rats, *Environ. Toxicol. Pharmacol.* **30**, 289-291.
[132] T.M. Saber, A.M.A. Abo-Elmaaty and H.M. Abdel-Ghany (2019). Curcumin mitigates mancozeb-induced hepatotoxicity and genotoxicity in rats, *Ecotoxicol. Environ. Saf.* **183**, 109467.
[133] L.D. Bobermin, D.O. Souza, C.A. Gonçalves and A. Quincozes-Santos (2018). Resveratrol prevents ammonia-induced mitochondrial dysfunction and cellular redox imbalance in C6 astroglial cells, *Nutr. Neurosci.* **21**, 276-285.
[134] G. Aviello, J.M. Canadanovic-Brunet, N. Milic, R. Capasso, E. Fattorusso, O. Taglialatela-Scafati, I. Fasolino, A.A. Izzo and F. Borrelli (2011). Potent antioxidant and genoprotective effects of boeravinone G, a rotenoid isolated from *Boerhaavia diffusa*, *PLoS One* **6**, e19628.
[135] V. Abalea, J. Cillard, M.P. Dubos, O. Sergent, P. Cillard and I. Morel (1999). Repair of iron-induced DNA oxidation by the flavonoid myricetin in primary rat hepatocyte cultures, *Free Radic. Biol. Med.* **26**, 1457-1466.

[136] O.H. El-Habit, H.N. Saada, K.S. Azab, M. Abdel-Rahman and D.F. El-Malah (2000). The modifying effect of β-carotene on gamma radiation-induced elevation of oxidative reactions and genotoxicity in male rats, *Mutat. Res.* **466**, 179-186.

[137] L. Potenza, C. Calcabrini, R. De Bellis, U. Mancini, L. Cucchiarini and M. Dachà (2008). Effect of quercetin on oxidative nuclear and mitochondrial DNA damage, *Biofactors* **33**, 33-48.

[138] B.N. Rao, P.R. Archana, B.K. Aithal and B.S. Rao (2011). Protective effect of zingerone, a dietary compound against radiation induced genetic damage and apoptosis in human lymphocytes, *Eur. J. Pharmacol.* **657**, 59-66.

[139] H. Wu, H. Zhang, C. Wang, Y. Wu, J. Xie, X. Jin, J. Yang and J. Ye (2011). Genoprotective effect of hyaluronic acid against benzalkonium chloride-induced DNA damage in human corneal epithelial cells, *Mol. Vis.* **17**, 3364-3370.

[140] B. Babazadeh, H.R. Sadeghnia, E. Safarpour Kapurchal, H. Parsaee, S. Nasri and Z. Tayarani-Najaran (2012). Protective effect of *Nigella sativa* and thymoquinone on serum/glucose deprivation-induced DNA damage in PC12 cells, *Avicenna J. Phytomed.* **2**, 125-132.

[141] H. Türkez and T. Sisman (2012). The genoprotective activity of resveratrol on aflatoxin $B_1$-induced DNA damage in human lymphocytes in vitro, *Toxicol. Ind. Health* **28**, 474-480.

[142] M. Alcaraz, D.G. Achel, A. Olivares, E. Olmos, M. Alcaraz-Saura and J. Castillo (2013). Carnosol, radiation and melanoma: A translational possibility, *Clin. Transl. Oncol.* **15**, 712-719.

[143] P. Vanitha, S. Senthilkumar, S. Dornadula, S. Anandhakumar, P. Rajaguru and K.M. Ramkumar (2017). Morin activates the Nrf2-ARE pathway and reduces oxidative stress-induced DNA damage in pancreatic beta cells, *Eur. J. Pharmacol.* **801**, 9-18.

[144] A. Leyva-Soto, R.A. Chavez-Santoscoy, L.R. Lara-Jacobo, A.V. Chavez-Santoscoy and L.N. Gonzalez-Cobian (2018). Daily consumption of chocolate rich in flavonoids decreases cellular genotoxicity and improves biochemical parameters of lipid and glucose metabolism, *Molecules* **23**, 2220.

[145] S. Gateva, G. Jovtchev, A. Stankov, A. Georgieva, A. Dobreva and M. Mileva (2019). The potential of geraniol to reduce cytotoxic and genotoxic effects of MNNG in plant and human lymphocyte test-systems, *S. Afr. J. Bot.* **123**, 170-179.

[146] T. Boran, A. Gunaydin, A.T. Jannuzzi, E. Ozcagli and B. Alpertunga (2019). Celastrol pretreatment as a therapeutic option against cisplatin-induced nephrotoxicity, *Toxicol. Res.* **8**, 723-730.

[147] S.K. Abraham, N. Schupp, U. Schmid and H. Stopper (2007). Antigenotoxic effects of the phytoestrogen pelargonidin chloride and the polyphenol chlorogenic acid, *Mol. Nutr. Food Res.* **51**, 880-887.

[148] S.K. Abraham, A. Eckhardt, R.G. Oli and H. Stopper (2012). Analysis of in vitro chemoprevention of genotoxic damage by phytochemicals, as single agents or as combinations, *Mutat. Res.* **744**, 117-124.

[149] S. Shruthi and K.B. Shenoy (2021). Gallic acid: A promising genoprotective and hepatoprotective bioactive compound against cyclophosphamide induced toxicity in mice, *Environ. Toxicol.* **36**, 123-131.

[150] E. Erikel, D. Yuzbasioglu and F. Unal (2019). In vitro genotoxic and antigenotoxic effects of cynarin, *J. Ethnopharmacol.* **237**, 171-181.

[151] S.L. Patil, N.B. Rao, H.M. Somashekarappa and K.P. Rajashekhar (2014). Antigenotoxic potential of rutin and quercetin in Swiss mice exposed to gamma radiation, *Biomed. J.* **37**, 305-313.

[152] M. Maatouk, N. Mustapha, I. Mokdad-Bzeouich, H. Chaaban, I. Ioannou, K. Ghedira, M. Ghoul and L. Chekir-Ghedira (2018). Heated naringin mitigate the genotoxicity effect of Mitomycin C in BALB/c mice through enhancing the antioxidant status, *Biomed. Pharmacother.* **97**, 1417-1423.

[153] A. Sehgal, M. Kumar, M. Jain and D.K. Dhawan (2011). Combined effects of curcumin and piperine in ameliorating benzo(a)pyrene induced DNA damage, *Food Chem. Toxicol.* **49**, 3002-3006.

[154] E.A. Safonova, K.A. Lopatina, A.V. Vychuzhanina, V.A. Mashanova, T.G. Razina, T.G. Borovskaya, E.P. Zueva, A.M. Gur'ev and M.V. Belousov (2018). Protective effect of polysaccharides from *Tussilago farfara* L. on bone marrow cells and small intestinal epithelium under conditions of polychemotherapy evaluated by DNA comet assay, *Bull. Exp. Biol. Med.* **166**, 217-221.

[155] D. Oliveira, C. Latimer, P. Parpot, C.I.R. Gill and R. Oliveira (2020). Antioxidant and antigenotoxic activities of *Ginkgo biloba* L. leaf extract are retained after in vitro gastrointestinal digestive conditions, *Eur. J. Nutr.* **59**, 465-476.

[156] A. Shetty, T. Venkatesh, P.S. Suresh and R. Tsutsumi (2017). Exploration of acute genotoxic effects and antigenotoxic potential of gambogic acid using *Allium cepa* assay, *Plant Physiol. Biochem.* **118**, 643-652.

[157] N. Quintero Ruiz, Y. Córdoba Campo, E.E. Stashenko and J.L. Fuentes (2017). Antigenotoxic effect against ultraviolet radiation-induced DNA damage of the essential oils from *Lippia* species, *Photochem. Photobiol.* **93**, 1063-1072.

[158] O. Szczepaniak, M. Ligaj, J. Kobus-Cisowska, M. Tichoniuk, M. Dziedziński, M. Przeor and P. Szulc (2020). The genoprotective role of naringin, *Biomolecules* **10**, 700.

[159] A. Emadi, R.J. Jones and R.A. Brodsky (2009). Cyclophosphamide and cancer: Golden anniversary, *Nat. Rev. Clin. Oncol.* **6**, 638-647.

[160] A. Basu, A. Bhattacharjee, A. Samanta and S. Bhattacharya (2015). Prevention of cyclophosphamide-induced hepatotoxicity and genotoxicity: Effect of an L-cysteine based oxovanadium(IV) complex on oxidative stress and DNA damage, *Environ. Toxicol. Pharmacol.* **40**, 747-757.

[161] C.C. Winterbourn (1995). Toxicity of iron and hydrogen peroxide: The Fenton reaction, *Toxicol. Lett.* **82-83**, 969-974.

[162] V. Cheewinthamrongrod, H. Kageyama, T. Palaga, T. Takabe and R. Waditee-Sirisattha (2016). DNA damage protecting and free radical scavenging properties of mycosporine-2-glycine from the Dead Sea cyanobacterium in A375 human melanoma cell lines, *J. Photochem. Photobiol B* **164**, 289-295.

[163] S. Hajra, A.R. Patra, A. Basu and S. Bhattacharya (2018). Prevention of doxorubicin (DOX)-induced genotoxicity and cardiotoxicity: Effect of plant derived small molecule indole-3-carbinol (I3C) on oxidative stress and inflammation, *Biomed. Pharmacother.* **101**, 228-243.

[164] O. Tacar, P. Sriamornsak and C.R. Dass (2013). Doxorubicin: An update on anticancer molecular action, toxicity and novel drug delivery systems, *J. Pharm. Pharmacol.* **65**, 157-170.

[165] F.A. Fornari, J.K. Randolph, J.C. Yalowich, M.K. Ritke and D.A. Gewirtz (1994). Interference by doxorubicin with DNA unwinding in MCF-7 breast tumor cells, *Mol. Pharmacol.* **45**, 649-656.

[166] I. Bouhlel, S. Kilani, I. Skandrani, R. Ben Amar, A. Nefatti, F. Laporte, I. Hininger-Favier, K. Ghedira and L. Chekir-Ghedira (2008). *Acacia salicina* extracts protect against DNA damage and mutagenesis in bacteria and human lymphoblast cell K562 cultures, *Nutr. Res.* **28**, 190-197.

[167] N. Kager, F. Ferk, M. Kundi, K.H. Wagner, M. Misík and S. Knasmüller (2010). Prevention of oxidative DNA damage in inner organs and lymphocytes of rats by green tea extract, *Eur. J. Nutr.* **49**, 227-234.

[168] H. Hosseinzadeh, A. Abootorabi and H.R. Sadeghnia (2008). Protective effect of *Crocus sativus* stigma extract and crocin (trans-crocin 4) on methyl methanesulfonate-induced DNA damage in mice organs, *DNA Cell Biol.* **27**, 657-664.

[169] F. Chaabane, I. Mokdad-Bzeouich, A. Sassi, N. Mustapha, R. Majouli, K. Ghedira and L. Chekir-Ghedira (2016). Genoprotective and neuroprotective effects of *Daphne gnidium* leaf methanol extract, tested on male mice, *Drug Chem. Toxicol.* **39**, 297-302.

[170] S. Wachtel-Galor, S.W. Choi and I.F. Benzie (2005). Effect of *Ganoderma lucidum* on human DNA is dose dependent and mediated by hydrogen peroxide, *Redox Rep.* **10**, 145-149.

[171] E. Turrini, C. Calcabrini, M. Tacchini, T. Efferth, G. Sacchetti, A. Guerrini, G. Paganetto, E. Catanzaro, G. Greco and C. Fimognari (2018). In vitro study of the cytotoxic, cytostatic, and antigenotoxic profile of *Hemidesmus indicus* (L.) R.Br. (Apocynaceae) crude drug extract on T lymphoblastic cells, *Toxins* **10**, 70.

[172] E. Asadpour, A. Ghorbani and H.R. Sadeghnia (2014). Water-soluble compounds of lettuce inhibit DNA damage and lipid peroxidation induced by glucose/serum deprivation in N2a cells, *Acta Pol. Pharm.* **71**, 409-413.

[173] A. Cabarkapa, L. Zivković, D. Zukovec, N. Djelić, V. Bajić, D. Dekanski and B. Spremo-Potparević (2014). Protective effect of dry olive leaf extract in adrenaline induced DNA damage evaluated using in vitro comet assay with human peripheral leukocytes, *Toxicol. In Vitro.* **28**, 451-456.

[174] M.V. Tamayo, A.P. Schuch, T. Yagura, L.B. Gil, C.F.M. Menck and A. Sánchez-Lamar (2018). Genoprotective effect of *Phyllanthus orbicularis* extract against UVA, UVB, and solar radiation, *Photochem. Photobiol.* **94**, 1026-1031.

[175] P.K. Mishra, G.V. Raghuram, A. Bhargava, A. Ahirwar, R. Samarth, R. Upadhyaya, S.K. Jain and N. Pathak (2011). In vitro and in vivo evaluation of the anticarcinogenic and cancer chemopreventive potential of a flavonoid-rich fraction from a traditional Indian herb *Selaginella bryopteris*, *Br. J. Nutr.* **106**, 1154-1168.

[176] P. Goswami, R. Banerjee and A. Mukherjee (2019). Potential antigenotoxicity assessment of *Ziziphus jujuba* fruit, *Heliyon* **5**, e01768.

[177] R. Del Pino-García, M.L. González-SanJosé, M.D. Rivero-Pérez and P. Muñiz (2012). Influence of the degree of roasting on the antioxidant capacity and genoprotective effect of instant coffee: Contribution of the melanoidin fraction, *J. Agric. Food Chem.* **60**, 10530-10539.

[178] M. Alcaraz, E. Olmos, M. Alcaraz-Saura, D.G. Achel and J. Castillo (2014). Effect of long-term 50 Hz magnetic field exposure on the micronucleated polychromatic erythrocytes of mice, *Electromagn. Biol. Med.* **33**, 51-57.