Zagazig Veterinary Journal, ©Faculty of Veterinary Medicine,
Zagazig University, 44511, Egypt.
Volume 52, Number 4, p:396-410 December 2024
DOI: 10.21608/zvjz.2024.299909.1248

REVIEW ARTICLE

Genotoxic Effect of Citalopram and Mitigating Impact of Ginseng and Vitamin D: A review Article

Gamal El-Din A. Shams[1], Gihan G. Moustafa[2], Reda M. Abd El-Aziz[3], Aya S. Mohamed[1*]
[1]Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, 44511, Egypt
[2]Department of Forensic Medicine and Toxicology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, 44511, Egypt
[3]Department of Physiology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, 44511, Egypt
* Corresponding author: Email: ayasalaheldin3@gmail.com

ABSTRACT

Depression is defined by its association with mood disorders, which are made up of groups of symptoms and signs, lasting from weeks to months. It leads to a major change in a person's regular ability to function, showing a pattern of recurring episodes. Deoxyribonucleic acid (DNA) damage that occurs in the nucleus, chromosomes, and DNA structure is referred to as a genotoxic effect. This includes insertions and breaks of DNA and abnormalities of genes and chromosomes. With the increasing prevalence of antidepressant drug use in current times, the determination of whether these medications induce genetic damage has become exceedingly crucial. Citalopram is a member of the selective serotonin reuptake inhibitors class of antidepressants, commonly prescribed for the management of depression.The Panax ginseng, a member of the Araliaceae family, has a long history of being utilized as a natural remedy. It has been known to decrease inflammation and combat free radicals, as well prevent age-related ailments, chronic fatigue, and issues related to digestion and cardiovascular health. Vitamin D plays a significant role in reducing the pro-oxidant systemic and tissue biomarkers associated with the onset, advancement, and reappearance of chronic cardiometabolic illness and cancer.Owing to numerous inconsistent findings on the antagonistic special effects and toxicities of SSRIs (particularly geno-toxicities), this review elucidates the genotoxic effects of these remedies, with a specific focus on citalopram, as well as reviewing modulating effect of ginseng and vitamin D on DNA damage.

***Keywords*:** Citalopram, Genotoxic effects, DNA damage, Ginseng, Vitamin D.

Introduction

In 2020, the World Health Organization (WHO) estimates that depression is projected to be the second leading cause of death attributable to diseases, following conditions associated with stress and cardiovascular issues [1]. Depression is an emotional ailment and a chief municipal fitness anxiety disturbing millions of people all-inclusive. It is a mutual syndrome that has been concomitant with numerous medical comorbidities frequently accompanying aging, such as type II diabetes, dementia, cerebrovascular and cardiovascular illnesses, as well as metabolic disorders [2].

Citalopram

Pharmacokinetics and pharmacodynamics

Pharmacokinetic studies examined the metabolism, safety, and tolerability of citalopram, paying particular attention to overdose, adverse reactions, and drug

interactions. They also examined the impact of citalopram on vulnerable groups, including patients with metabolic illnesses, the elderly, and children. Citalopram exhibits a more targeted and selective pharmacological profile compared to other antidepressants in the same class, making it well-tolerated with minimal drug interactions. Its efficacy extends to the treatment of major depression, other depressive disorders, and panic disorder [7]. It has the capability to effectively treat a range of anxiety disorders and various depressive disorders , and it also has the potential to be beneficial in numerous medical conditions. The liver's cytochrome P450 system metabolizes the selective serotonin reuptake inhibitors (SSRIs). The enzyme cytochrome P450 (CYP) 2C19, which is highly polymorphic and well-known to produce inter-individual variations in pharmacokinetics, is principally responsible for the metabolism of citalopram. When taken orally, citalopram absorbs rapidly; the plasma half-life is approximately thirty five hours, and peak plasma levels are typically attained 1-4 hours after delivery [8]. The half-lives of each SSRI in a steady state vary depending on the medication. Citalopram, for instance, has a half-life of roughly 26 hours [7]. The pharmacokinetics of citalopram are briefly reviewed in this summary (**Figure1**), along with a discussion of the potential pharmacogenes implicated.

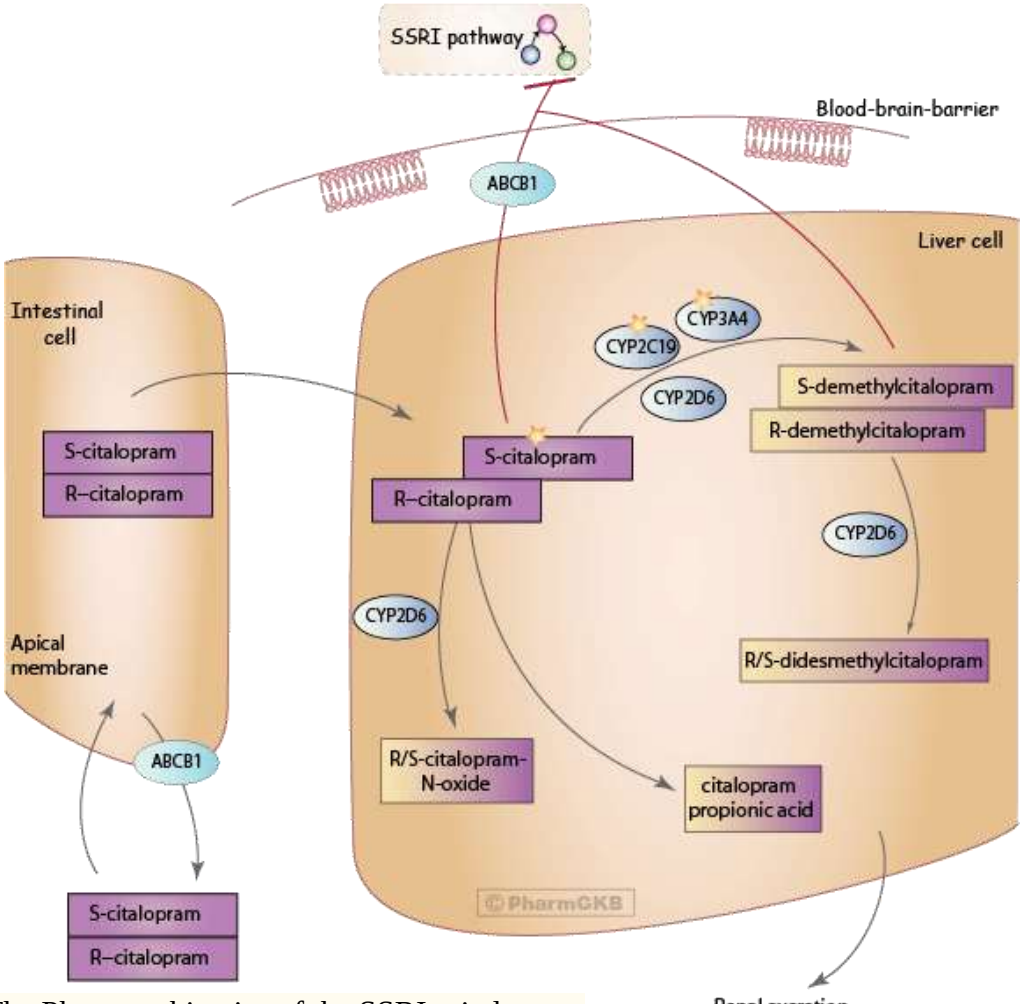

Figure1. The Pharmacokinetics of the SSRIs citalopram (PA164713429; http://www.pharmgkb.org/do/serve?objId=PA164713429&objCls=Pathway). SSRI, selective serotonin reuptake inhibitor.

Uses, mechanism of action, and side effects

Citalopram is unique of most widely used antidepressants . It is commonly used as a first-line treatment for depression. In the USA, antidepressants are solitary of the greatest ordinarily used therapeutic drug classes [2]. Antidepressants refer to psychiatric medications, dietary substances, or herbal materials (such as herbs, leaves, or fruits) used to alleviate conditions like depression or dysthymia (chronic depression). However, the widely held of these prescriptions are engaged to cure depression. Antidepressants can also be taken to treat other conditions, such as anxiety disorders. The WHO has calculated that approximately 350 million individuals across all age groups are affected by major depressive disorder (MDD), a condition linked to overall disability and higher mortality rates. Selective serotonin reuptake inhibitors (SSRIs) have emerged as the most frequently recommended medication class for treating MDD [1-3]. Their mode of action involves the binding of the serotonin transporter (SERT), which inhibits the reuptake of serotonin (5-HT) and leads to elevated 5-HT levels in the extracellular area. Despite this neurochemical effect, the exact way in which SSRIs enhance depressive symptoms is still not fully understood. This is particularly puzzling given that symptom relief typically occurs after a delay of a few weeks, and not all individuals show a positive response to initial treatment [2, 4]. In addition to its ability to alleviate depression, citalopram is prescribed for the treatment of anxiety, panic disorders, obsessive-compulsive disorder, and behavioral abnormalities associated with dementia. Similar to other SSRIs, temporary nausea is a frequent side effect, and decreased libido and sexual dysfunction may occur following citalopram treatment; nevertheless, patients can endure these adverse reactions. [3, 4]. Newly, it has been described that SSRIs may affect the parameters in semen and play an imaginable part in the etiology of infertility in males. SSRIs are commonly prescribed ADPS supplementary with an augmented hazard of male fertility. Majority of the available studies are focused on SSRIs such as citalopram, escitalopram, paroxetine, sertraline, fluvoxamine, and fluoxetine, which have shown negative impacts on the reproduction. Citalopram, sertraline, and fluoxetine are processed to complexes having analogous belongings as the maternal medicines, whereas this is not the case with the metabolites of fluvoxamine and paroxetine [5].

Treatments with citalopram resulted in sexual- dysfunction (reduction in arousal and libido) and 2 to 10% anorgasmia in thirty percent of patients. Administration of citalopram for short and long periods to rat's males diminishes ejaculation and mounting. Previous reports show that SSRI treatment increases the risk of sexual dysfunction by 25–73%, compared to other antidepressant treatments [6]. SSRIs can produce some adverse effects, such as nausea, headaches, weight gain, erectile dysfunction and diminished libido. Citalopram hydrobromide (CTL) has been publicized in abundant studies to cause sexual dysfunction in male rats given doses of 5 and 10 mg/kg of CTL. The male rats also showed increased sperm morphology abnormalities, levels of luteining (LH) and testosterone hormones, and sperm DNA damage, as well as reduced sperm concentration and glutathione levels. The fall in sperm concentration is accompanied by a change in blood hormone levels, which can be interpreted as a compensatory mechanism against this decline. The LH and testosterone hormones stimulate the process of spermatogenesis. Human studies from an

infertility clinic showed that the concentration of sperm is inversely correlated (negatively) with the serum levels of follicle-stimulating hormone (FSH) and LH. Abundant investigations have verified that citalopram hydrobromide is an SSRI with little effects on the reuptake of dopamine and norepinephrine in neurons. Previous investigations go over the citalopram's indications, mechanism of action, administration, contraindications, monitoring, and toxicity [5**,** 6].

Genotoxic effect of citalopram

The recombinogenic potential of citalopram in *Aspergillus nidulans* may be linked to the recombinational repair of citalopram-induced breaks in DNA strands, given that citalopram has been previously identified as an inhibitor of DNA synthesis. Numerous acute and long-term pathophysiological conditions, including endothelium damage and cancer, can be caused by damage to DNA. A recent study assessed the in vivo DNA damage caused by the antidepressant medication citalopram at human dosage recommendations in mouse somatic cells. The amount of DNA strand breakage and micronuclei growth increased significantly in mice administered citalopram at varying oral dosages of 12 or 24 mg kg–1 for 7 days, according to a bone marrow comet assay and a micronucleus test. Accumulation of reactive oxygen species (ROS) and free radicals can damage biomolecules, such as DNA which is one of the critical factors in the genetic susceptibility to diseases. Citalopram causes significant differential DNA methylation ($P < 0.01$) in 626 gene promoters [7- 9].

Because DNA damage can trigger a variety of disease processes, such as cancer, aging, neurodegeneration, cardiovascular disease, and other tissue toxicities, genotoxicity has attracted a lot of attention [10]. It has previously been shown that sertraline had a lower proportion of genotoxicities than citalopram and fluoxetine [2].

The methods for detection of DNA damage

Alkaline gel electrophoresis and pulsed field gel electrophoresis are two electrophoresis methods used to evaluate DNA damage. Specialized gel analysis software is used for the majority of the measurement and analysis. Generally, DNA gel electrophoresis is only utilized following PCR amplification of DNA [11]. One effective technique for determining the early phases of DNA damage at the single-cell level is single-cell gel electrophoresis, also referred to as the comet assay. Since then, it has grown in acceptance as a common method for genotoxicity testing, biomonitoring, and assessing DNA damage and repair [10]. The comet assay can be used to detect potential human mutagens and carcinogens as a genotoxicity test [12]. Elevated micronuclei (MN) occurrence is indicative of the risk of developing cancer in humans, and the micronuclei assay has been extensively employed to measure unaddressed genetic harm [13]. If methods are implemented to enable the visualization of complete chromosomes within MN, the identification of MN could serve as a tool for detecting numerical chromosomal abnormalities induction, since MN can result from chromosome breakage or lagging chromosomes. There are several methods available to differentiate between MN caused by clastogens and aneugens; however, the most accurate approaches are those that identify centromeres, like the fluorescence in situ hybridization (FISH) test. As stated in the guidelines of the International Program on Chemical Safety (IPCS), the comet assay, MN test, and FISH procedures are some of the most often studied gene toxicity outcomes for the monitoring of the genotoxic effects of carcinogens in humans [14]. Popular test systems for detecting genotoxic effects are the comet assay and the MN test. A test's ability to generate chromosome and/or genome defects can

be evaluated using the MN test, while its ability to break DNA strands can be directly measured using the comet assay.

In conclusion, the aforementioned data suggest that citalopram is a genotoxic drug that causes genomic damage that result in MN, or olive tail moment [9]. The citalopram genotoxic reactions seen in these Chinese hamster lung fibroblasts are consistent with positive responses for chromosomal abnormalities and bacterial reverse mutations in *S.* Typhimurium TA98 and TA1537 [15].

Herbal plants might act as a powerful natural antioxidant, for instance, ginseng effectively modulates apoptosis by reducing the excessive inflammatory response in acute or chronic inflammation [16]. Therefore, this review was extended to focus on the role of ginseng as a powerful antioxidant.

Ginseng

Active components and pharmacological effects of ginseng

Ginseng, scientifically known as Panax ginseng C. A. Meyer, is a perennial plant classified under the *Araliaceae* family. The genus *Panax*, first used by the Russian botanist, Carl A Meyer, is derived from the Greek *pan*, meaning "all", and *axos*, meaning "medicine", indicating that ginseng is a cure for all diseases [17].

Its key components consist of ginsenosides, polysaccharides, amino acids, volatile oil, and polyacetylene. The root of ginseng, specifically Korean or Asian ginseng, has been highly regarded as a significant traditional medicine in East Asian nations such as China, Korea, and Japan for over two millennia. Throughout history, ginseng has earned the title of the "king of herbs" and has been extensively utilized for the treatment of various ailments [16]. Ginseng's active components, such as saponins, polysaccharides, and active peptides, exhibit antioxidant, anti-apoptotic, neuroprotective, and age-delaying properties. In particular, research has demonstrated the potent immunomodulatory and anti-inflammatory properties of ginseng and ginsenosides in the digestive tract [18]. The primary constituents of ginseng are called ginsenosides, or ginseng saponins, and they are divided into two main groups based on the nature of their aglycones: protopanaxadiol (PPD) and protopanaxatriol (PPT). In the past, *Panax ginseng* modulated oxidative stress, DNA damage, caused inflammations, and apoptosis in rats [19]. According to another study, ginseng has a number of important non-saponin components, such as vitamins, peptides, amino acids, polyacetylenic alcohols, essential oils, and polysaccharides. Following administration of ginseng extract orally to both humans and rats, a new ginseng saponin metabolite known as 20-O-(h-D-glucopyranosyl)-20(S)-protopanaxadiol (IH-901) has been recently discovered and isolated. This metabolite is derived from ginsenosides Rb1, Rb2, and Rc. IH-901 has exhibited antigenotoxic and anticlastogenic properties in rats co-treated with benzo(a)pyrene and has also shown to enhance the effectiveness of anticancer drugs in cancer cell lines that were previously resistant to various anticancer therapies. Because plant polysaccharides typically exhibit anticancer effects through modification of innate immunity, ginseng polysaccharides have also been the subject of chemical and biological investigation [17]. Ginseng has been utilized for its antioxidant properties, immune system stimulation, stress relief, and central nervous system (CNS) function. Its pharmacological effects have been shown in cancer, diabetes, and cardiovascular illnesses [18, 20]. Further investigations have revealed that ginseng's active ingredients lessen endogenous DNA damage, enhance the oxidation/antioxidation balance, and lower the generation of ROS [18].

Plants have been the basis of traditional medicines throughout the world for thousands of years and continue to provide new remedies to humankind; a

great deal of effort has therefore focused on using available experimental techniques to identify natural antioxidants from plants. Several authors have reviewed the beneficial uses of these plant species.

Ginseng and DNA Damage

The main cause of aging is DNA damage, and the mechanism by which ginseng's active ingredients prevent and slow down aging has not yet been thoroughly studied [17]. DNA damage is primarily classified into 2 categories: exogenous damage, which is caused by external factors such as chemicals and ionizing radiation, and endogenous damage, which happens spontaneously and is induced by internal factors within the organism such as ROS and cellular metabolic byproducts [20,21]. The primary source of ROS in cells is the mitochondrial respiratory chain. [22]. ROS have the ability to oxidize nucleoside bases, attack DNA molecules' double bonds, and result in breakage in either single- or double-stranded DNA [23]. Overproduction of ROS leads to intracellular dysregulation of oxidative/antioxidative processes, resulting in oxidative stress and additional DNA damage [24].

A previous study revealed that damage to DNA has been implicated in the development of numerous aging-related illnesses, including cancer [25]. Oxidative stress can result in genetic mutations, chromosomal instability, altered gene expression, and DNA damage, all of which can contribute to the development of cancer. Antioxidant-rich diets and supplements have been shown to reduce DNA damage; however there is a negative association between antioxidant levels and DNA damage. The volunteers would be supplemented with commercial ginseng extract. Chinese turnip would be included in or excluded from the analysis of ginseng's DNA-protective effect on human lymphocytes. When cooked turnip was consumed at the same time as ginseng extract, the protective effect against DNA damage caused by H_2O_2 was offset [25].

The bioactive constituents found in ginseng have the ability to enhance the function of DNA glycosylases and sirtuin family members within the DNA damage repair system, thus aiding in the repair of DNA damage, while also blocking the cGAS-STING pathway [26]. According to a previous study, American ginseng extract can prevent both in vitro and in vivo leukocyte activation and the ensuing damage to epithelial cell DNA [27]. Further investigations revealed that the potent genotoxic chemical ginsenoside Rg3 damages DNA in human osteosarcoma cells. Furthermore, normal human cells were shielded from DNA damage and apoptosis by ginsenoside Rg3 [28]. Ginseng decrease CYP oxidative changes by restoring metabolic functional indicators, increasing antioxidant status, lowering inflammatory response, and improvement of molecular docking assessment. Additionally, it has been found to alleviate the extent of histopathological modifications and enhance the immunohistochemistry labelling of Bcl-2 and caspase-3 proteins in kidney and liver tissues [29]. Other investigations evaluated the antioxidant properties and protective effects of Korean red ginseng extract (KGE) on aflatoxin-induced oxidative stress and DNA damage in rats. The researchers determined that KGE exhibits a strong protective effect against aflatoxin-induced oxidative stress and DNA damage, suggesting its potential use in regions with high aflatoxin contamination. Animals that were given a diet contaminated with AFs and then treated with KGE exhibited a notable enhancement in micronucleated polychromatic erythrocytes (Mn-PCEs), polychromatic erythrocytes (PCEs) percentage, DNA fragmentation, glutathione (GSH) and decrease lipid peroxidation (LP) in liver [30]. *Panax ginseng* extracts obtained using various methods contain a range of ginsenosides

that improve arrhythmia, reduce cardiac damage, improve mitochondrial dysfunction, suppress oxidative stress, and apoptosis [31]. Furthermore, ginsenosides may also decrease the amount of oxygen radicals produced by intracellular metabolism, which is crucial for preserving cell viability by inducing antioxidant enzymes. In general, ginseng is protective against aflatoxins-induced liver damage and contributes to reduce oxidative damage to nucleic acids in the body and boosting antioxidant state [30].

According to literature, one pathological alteration that is commonly observed in the early stages of Alzheimer's disease is mitochondrial dysfunction. Typically, neuronal degeneration, apoptosis, and synaptic dysfunction result from mitochondrial injury [32]. The impact of signaling pathways on apoptosis and anti-apoptosis proteins is primarily accountable for P. ginseng's capacity to improve mitochondrial harm [33]. The mitochondrial membrane contains the vital anti-apoptotic molecules Bcl-2 and Bcl-xl, but the apoptotic promoter Bax, which is phylogenetically similar to Bcl-2, can initiate the release of cytochrome C (Cyt C), the production of caspase-3, and subsequently, apoptosis [34]. Additional research has demonstrated that Bax and Bcl-2 can control mitochondrial membrane permeability via modifying the mitochondrial permeability transition pore (MPTP), as well as inhibiting the release of mitochondrial cytochrome C (Cyt C). Bax and Bcl-2 can exert their anti-apoptotic actions through both of the ways mentioned above, preventing cell death [35]. In order to prevent mitochondrial damage, it is crucial to increase the expression of Bcl-2 and Bcl-xl, decrease level of Bax and caspase-3, and minimize the release of Cyt C. Research has shown that ginsenoside CK can boost Bcl-2 expression and reduce the expression of Bax and caspase-3 [33].

Many biological activities of ginsenosides are known to exist, such as immune modulation regulation, protection in the central nervous and cardiovascular systems, anti-aging, anti-carcinogenic, anti-fatigue, anti-pyretic, anti-stress, and promoting activities related to DNA, RNA, and protein synthesis [36].

In the animal model, the testis of rats exposed to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin were assessed for DNA damage and reproductive toxicity. The group treated with ginseng extracts exhibited a notable decrease in DNA damage levels and reduced pathological effects. Our previous study also demonstrated the impact of ginseng on DNA damage in humans [37]. A number of papers have suggested processes by which one of the ginsenosides included in KGE, ginsenoside Rh2 (GS-Rh2), has been shown through mechanisms suggested in a number of papers to be vital in the management and prevention of liver cancer [30].

After eight weeks of ginseng treatment, the Comet assay demonstrates reduced damage to lymphocyte DNA and increased levels of antioxidant enzymes [38]. According to earlier findings, ginseng extract consumption might dramatically boost lymphocyte DNA tolerance to oxidative stress in as little as two hours. This may be indicated by the fact that comet scores for H_2O_2 treated cells in blood samples obtained after ginseng ingestion were much lower than those obtained before ingestion [25].

Vitamin D

Physiology and metabolism of vitamin D

Calciferol, or vitamin D is a lipid-soluble vitamin that plays an important function in the development of healthy bones, proper calcium levels, and phosphorus-calcium metabolism. Classes of liposoluble steroid chemicals with similar chemical structures and biological effects that come from many sources are collectively referred to as vitamin D. The two most important vitamin D components are cholecalciferol, also known as vitamin D3, and ergocalciferol,

or vitamin D2. A combination of vitamin D2 and lumisterol was previously known as vitamin D1. Vitamin D2 is created by irradiating ergosterol in yeast, but vitamin D3 is produced from 7-dehydrocholesterol after ultraviolet-B irradiation in human skin. This is a distinct property of vitamins [39–41]. The body uses a complicated set of processes to generate vitamin D. First, it converts the cholesterol precursor molecule 7-dehydrocholesterol into the precursor of vitamin D hormone, cholecalciferol (vitamin D3), in response to ultraviolet light. Thus, vitamin D isn't technically considered a vitamin. After that, vitamin D3 is hydroxylated in the kidney to produce 1,25-dihydroxycholecalciferol, or calcitriol, which is the most biologically active hormone form of this compound. Additionally, it is hydroxylated in the liver to produce 25(OH) D3. The primary method for inactivating calcitriol and other vitamin D molecules is 24-hydroxylation, which results in 1,24,25(OH) cholecalciferol and is mostly carried out in the kidney [39]. Additional research revealed that the skin converts 7-dehydrocholesterol into vitamin D3, or cholecalciferol, the natural form of vitamin D. After being exposed to radiation, 7-dehydrocholesterol converts to pre-vitamin D3, which then changes its structure by undergoing a temperature-sensitive rearrangement of three double bonds. The skin's production is the primary source of vitamin D, dependent on the intensity of Ultraviolet (UV) light and affected by factors such as latitude and season. Gene regulation is directly impacted by the transcription factor vitamin D receptor, which is bound and induced by 1, 25 (OH) 2 D3. There has been a growing focus on vitamin D due to the reemergence of vitamin D deficiency and rickets as significant global health issues. Additionally, research in the laboratory has provided compelling evidence that 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], the active hormonal form of vitamin D, elicits various biological responses beyond skeletal health. These responses include impacts on the cardiovascular system, potential for multiple sclerosis and inflammatory bowel disease prevention, as well as the ability to hinder the advancement of breast, colon, and prostate cancer cells [39]. The 1,25(OH)2D3 activated vitamin D receptor/retinoic X receptor (VDR/RXR) heterodimeric complex directly binds to specific DNA regions, which is the genomic mechanism of 1,25(OH)2D3 action. Additionally, various VDR co-regulatory proteins have been identified, and genome-wide studies have revealed that 1,25(OH)2D3 regulates gene activity at multiple sites located several kilobases away from the transcription start site [40].

Through its metabolites, vitamin D facilitates the release of calcium from the bones in the absence of consumption, triggers osteoblasts to generate receptor activator nuclear factor-κB ligand (RANKL), leading to the activation of dormant osteoclasts for bone resorption (osteoclastogenesis), and elevates serum calcium levels by promoting active intestinal calcium absorption. The equilibrium of calcium and phosphorus is continuously maintained by vitamin D and parathyroid hormone [40].

The absorption of vitamin D takes place in the small intestine; however, the specific section of the intestine responsible for this process remains unidentified in humans. In rats, the ileum serves as the principal site of absorption. Proteins mediate the absorption of non-hydroxylated vitamin D at dietary doses. Three intestinal cell membrane proteins—Niemann-Pick C1-Like 1 (NPC1L1), cluster of differentiation 36 (CD36), and scavenger receptor class B type 1 (SR-B1) are engaged at the apical side. After absorbed, vitamin D is integrated into chylomicrons that are released into lymphatic capillaries, avoiding first-pass metabolism in the process. Lipoprotein lipase may facilitate the transportation and rapid storage of a portion of the vitamin D present in chylomicrons in

skeletal muscles and adipose tissues. The health of muscles also depends on vitamin D levels. Furthermore, some findings imply that vitamin D can lessen the loss of pancreatic beta-cells, hence preventing the occurrence of autoimmune-based diabetes [41]. Within the cardiovascular system, vitamin D has been shown to lower both systolic and diastolic blood pressure in individuals with hypertension, while a high vitamin D level is linked to a 50% reduction in the risk of cardiovascular mortality [42, 43]. It also modulates the immune system, and low vitamin D levels cause immunological dysfunction and an increased risk of infectious infections [44]. Adequate levels of vitamin D are essential for the proper functioning of the nervous system. Research has shown a correlation between vitamin D deficiency and the incidence of multiple sclerosis (MS). An elevated level of vitamin D was linked to a lower occurrence of MS, while a deficient vitamin D status was linked to a higher occurrence of this condition [40].

Vitamin D and DNA damage

Maintaining DNA integrity may also benefit from adequate vitamin D levels. One way to categorize vitamin D's job is that it has two main functions: it protects DNA from damage and controls cell proliferation. A clinical research showing that vitamin D administration reduced the level of oxidative damage marker 8-hydroxy-2'-deoxyguanosine in colorectal epithelial crypt cells suggests that vitamin D may be able to prevent oxidative damage to DNA in humans. Research using various cell types and animal models has also demonstrated a significant decrease in chromosomal abnormalities and oxidative stress damage, Additionally, vitamin D administration also prevents telomere shortening and inhibits telomerase activity. Vitamin D also plays a secondary role in regulating the activity of poly-ADP-ribose polymerase in the DNA damage response pathway, which is crucial for detecting DNA lesions and preventing DNA damage. Additionally, it has the ability to control apoptosis to encourage cell death and the cell cycle to stop damaged DNA from proliferating. If it is true that vitamin D prevents DNA damage, it may help preventing human colorectal cancer, although there isn't much evidence to support this theory. Due to the paucity of human evidence, it is unclear how much vitamin D should be taken to minimize DNA damage [45]. The majority of revisions discovered a protective correlation between a high enough level of vitamin D and a decreased risk of cancer. Increased plasma vitamin D levels have been shown to significantly lower the incidence rates of several cancers, including those of the colon, breast, ovarian, kidney, pancreatic, prostate, and other tissues. Previous research suggests that taking vitamin D supplements may lower the chance of developing some malignancies, such as pancreatic and breast cancer [45].

Previously, it is recognized that any alteration to the physical or chemical structure of DNA is referred to as DNA damage. Numerous exogenous and endogenous stimuli, including chemicals, radiation, and free radicals, might increase this damaging effect. It has been discovered that non-malignant cells from cancer patients can exhibit genome instability in addition to tumor cells. Clinical and preclinical evidence demonstrating the critical role DNA damage responses play in the genesis, growth, and spread of cancer [46].

Globally, vitamin D insufficiency is very common, and there may be significant implications for its link to DNA damage. While vitamin D supplementation may have a pro-oxidant effect, reduce the risk of viral infections, and stop tumor growth, vitamin D insufficiency increases DNA damage [47]. Damage to DNA brought on by oxidation can result in phenotypic alterations, mutations, and apoptosis. Potential treatments for illness prevention are provided by agents that prevent such

harm. Vitamin D deficiency was found to increase DNA damage in the mononuclear cells of severely asthmatic people, while vitamin D therapy was found to reduce DNA damage in type 2 diabetic mice [48]. A preceding study assessed different vitamin D analogs in relation to bleomycin-induced DNA damage. In a range of animal models, bleomycin can cause lung fibrosis and fibrogenic cytokine production by oxidant-mediated DNA scission [48]. Over the years, a significant number of vitamin D analogs have been created, and several of them have been licensed for clinical use in the treatment of psoriasis, osteoporosis, and secondary hyperparathyroidism [49]. Vitamin D cannot be used as a treatment for many illnesses due to its strong effects on intestinal calcium and phosphorus absorption and bone mineral mobilization, which frequently result in the development of hypercalcemia and hyperphosphatemia. The perfect analog would still be able to attach to vitamin D receptors and have little impact on the metabolism of calcium and phosphorus [48]. Previously,, hypocalcemic vitamin D analogs may exhibit a lower rate of DNA damage expression following a bleomycin shock than does the active form of vitamin D [50].

In a previous report, it was shown that 1,25 vitamin D3 provided a protection against DNA damage caused by UV 1,25VD3 and its low-calcemic analogues were found to reduce the formation of cyclobutane pyrimidine dimers (CPDs) in human keratinocytes exposed to UV [51]. Scientists believe that the main factor contributing to this protective effect against the creation of pyrimidine dimers is the well-documented antiproliferative properties of 1,25VD3. This is thought to be linked to the inhibition of cell growth induced by cell cycle arrest, a condition that results in more condensed DNA that is less susceptible to DNA-damaging agents. Furthermore, it has been demonstrated that 1,25VD3 influences the expression of Bcl-2-family proteins, such as Bcl-2, Bax, and Bad, and the correlation between their expression levels indicates that it has anti-apoptotic properties [52]. Plentiful other studies demonstrated how nitric oxide influences DNA repair [53]. Therefore, by reducing nitric oxide production, 1,25VD3 can affect DNA repair, including nucleotide excision repair (NER) In addition to decreasing the amount of nitric oxide products, 1,25VD3 also upregulated p53 expression, indicating that it is involved in DDR, which includes DNA repair [54].

Research conducted both in laboratory settings and in living organisms demonstrates that vitamin D compounds enhance the effectiveness of numerous anticancer drugs. The combination of calcitriol or other 1,25(OH)D3 with platinum compounds has been shown to significantly increase the potency of these agents, often resulting in a synergistic effect. This enhanced efficacy is linked to higher levels of p21 expression, disruption of cell cycle progression, improved apoptosis induction, and elevated p73 expression [55].

A number of molecular studies were applied regarding vitamin D's function in preventing tumor cell growth, proliferation, and invasiveness as well as cell cycle arrest and inflammatory signaling. Vitamin D may also control the cancer microenvironment by activating various molecular pathways. More recently, a function in controlling the growth of cancer stem cells and the expression of short non-coding microRNAs (miRNAs) has been discovered, giving vitamin D a more significant role in the initiation and advancement of cancer [56].

Studies reveal that vitamin D3 levels can affect the risk of reactive oxygen species (ROS)-induced DNA damage in hypertensive persons relative to normal blood pressure individuals. Research has shown that diets rich in (10 000 IU/kg) or low in (0 IU/kg) vitamin D3 might decrease ROS production and DNA

damage in spontaneously hypertensive rats (SHR) and normotensive control Wistar-Kyoto (WKY) rats during a 12-week treatment period [57]. The ROS have the ability to react with DNA to produce chromosomal damage, double- and single-strand breaks, and other DNA lesions. They can also oxidize proteins, lipids, and DNA, which can lead to cellular malfunction [57]. Furthermore, it has been demonstrated that low levels of vitamin D3 raise blood pressure, but sufficient amounts of vitamin D3 (defined as 25-hydroxyvitamin D3 levels between 20 and 30 ng/mL) lower blood pressure or maintain normal blood pressure [58]. Neutrophils are the primary generators of (ROS) in circulation through the activation of the enzyme complex NADPH oxidase, which serves as the main source of superoxide anion in the peripheral vasculature [59]. While low levels of vitamin D3 can cause ROS to be produced, as well as induce DNA and chromosomal damage, vitamin D3 can also control cellular processes related to redox equilibrium and the body's reaction to ROS formation [57].

Conclusions

Numerous acute and chronic pathophysiological diseases can result from damage to DNA. bases on reviewd results, Citalopram causes DNA harm and is a genotoxic substance. Its antidepressant and sedative effects are potentiated by ginseng, and vitamin D. The effectiveness of ginseng in treating a variety of illnesses, including cancer, neurological, cardiovascular, viral, and metabolic disorders was documented.. Ginseng functions as an immunomodulator, regulating the innate and adaptive immune systems to combat infections, and is crucial for maintaining calcium, phosphate, and bone homeostasis, that can influence DNA nucleotide excision. Besides,studies on animal and cell culture models have produced noteworthy data that emphasize the significance of vitamin D and its anti-inflammatory function in the prevention of cancer. Finally,One can take into account multiple routes in 1,25VD3's defense mechanism against DNA damage.

Conflict of Interests

The authors have declared that they have no potential conflicts of interest.

References

[1] Yaman, H.M. and Erbaş, O. (2023): Genotoxic effects of commonly used selective serotonin reuptake inhibitors antidepressants. J Exper Basic Med Sci, 4(3):170-174.

[2] Ahmadimanesh, M.; Abbaszadegan, M.R.; Hedayati, N.; Yaz dian-Robati, R.; Jamialahmadi, T. and Sahebkar A (2021): A systematic review on the genotoxic effects of selective serotonin reuptake inhibitors. Adv Exp Med Biol, 115-124.

[3] Pollock, B.G. (2001): Citalopram: a comprehensive review. Expert Opin Pharmacother, 2: 681–698.

[4] Sloot, W.N.; Bowden, H.C. and Yih, T.D. (2009): In vitro and in vivo reproduction toxicology of 12 monoaminergic reuptake inhibitors: possible mechanisms of infrequent cardiovascular anomalies. Reprod Toxicol, 28: 270–282.

[5] Fikret, E.; Atilgan, D.; Firat, F.; Markoc, F.; Parlaktas, B.S. and Sogut, E. (2014): The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats', International Braz J Urol, 40: 100-08.

[6] Ilgin, S.; Kilic, G.; Baysal, M.; Kilic, V.; Korkut, B.; Ucarcan, S. and Atli, O. (2017): Citalopram induces reproductive toxicity in male rats. Birth Defects Res, 109: 475-85.

[7] Kanherkar, R.R.; Getachew, B.; Ben-Sheetrit, J.; Varma, S.; Heinbockel, T.; Tizabi, Y. and Csoka, A.B. (2018): The effect of citalopram on genome-wide DNA methylation of human cells. Int J Genomics, 2018:8929057.

[8] Franco, C.C.; Castro-Prado, J.; Rosada, L.J.; Sant'Anna, J.R. and Castro-Prado, M.A. (2010): Mitotic recombination: a genotoxic effect of the antidepressant

citalopram in Aspergillus nidulans. Exp Biol Med (Maywood), 235(10):1257-62.

[9] Attia, S.M.; Ashour, A.E. and Bakheet, S.A. (2013): Comet-FISH studies for evaluation of genetic damage of citalopram in somatic cells of the mouse. J Appl Toxicol, 33(9):901-905.

[10] Kastan, M.B. (2008): DNA damage responses: mechanisms and roles in human disease: 2007 Clowes GHA. Memorial Award Lecture. Mol Cancer Res, 6: 517–524.

[11] Draz, E.I.; Emara, A.M.; Saad, K.M.; Badaway, A.; El-Nabi, H.S.E. and Abd – Elgelil, H. (2009): Genotoxicity of some commonly used antidepressants (fluoxetine, sertraline and clomipramine). Mansoura J. Forensic Med Clin Toxicol, 17: 63-78.

[12] Collins, A.R. and Azqueta, A. (2012): DNA repair as a biomarker in human biomonitoring studies; further applications of the comet assay. Mutat Res, 736: 122–129.

[13] Anderson, D.; Yu, T-W. and McGregor, D.B. (1998): Comet assay responses as indicators of carcinogenic exposure. Mutagenesis, 13: 539–555.

[14] Bonassi, S.; Znaor, A.; Ceppi, M.; Lando, C.; Chang, W.P.; Holland, N.; Kirsch-Volders, M.; Zeiger, E.; Ban, S.; Barale, R.; Bigatti, MP.; Bolognesi, C.; Cebulska-Wasilewska, A.; Fabianova, E.; Fucic, A.; Hagmar, L.; Joksic, G, Martelli, A.; Migliore, L.;Mirkova, E.; Scarfi, M.R.; Zijno, A.; Norppa, H. and Fenech, M. (2007): An increased micronucleus frequency in peripheral blood lymphocytes predicts the risk of cancer in humans. Carcinogenesis, 28: 625–631.

[15] Albertini, R.J.; Anderson, D.; Douglas, G.R.; Hagmar, L.; Hemminki, K, Merlo F.; Natarajan, AT.; Norppa, H.; Shuker, D.E.; Tice R.; Waters, M.D. and Aitio, A. (2000): IPCS guidelines for the monitoring of genotoxic effects of carcinogens in humans. International Programme on Chemical Safety. Mutat Res, 463: 111–172.

[16] Leung, K.W. and Wong A.S. (2010): Pharmacology of ginsenosides: A literature review. Chin Med, 5: 20.

[17] Zhao, L.; Zhang, T. and Zhang, K. (2024): Pharmacological effects of ginseng and ginsenosides on intestinal inflammation and the immune system. Front Immunol, 15:1353614.

[18] Su, J.; Su, Q.; Hu, S.; Ruan, X. and Ouyang, S. (2023): Research progress on the anti-aging potential of the active components of ginseng. Nutrients, 15(15): 3286.

[19] El-Demerdash, F.M.; El-Magd, M.A. and El-Sayed, R.A. (2021): Panax ginseng modulates oxidative stress, DNA damage, apoptosis, and inflammations induced by silicon dioxide nanoparticles in rats. Environ Tox, 36(7):1362-1374.

[20] Tubbs, A. and Nussenzweig, A. (2017): Endogenous DNA damage as a source of genomic instability in cancer. Cell, 168:644–656.

[21] Jackson, S.P. and Bartek, J. (2009): The DNA-damage response in human biology and disease. Nature, 461:1071–1078.

[22] He, B.; Chen, D.; Zhang, X.;Yang, R.; Yang, Y.; Chen, P. and Shen, Z. (2022): Oxidative stress and ginsenosides: An update on the molecular mechanisms. Oxid. Med. Cell Longev, 2022: 9299574.

[23] Srinivas, U.S.; Tan, B.W.Q.; Vellayappan, B.A. and Jeyasekharan, A.D. (2019): ROS and the DNA damage response in cancer. Redox Biol, 25:101084.

[24] Carusillo, A. and Mussolino, C.D.N.A. (2020): DNA Damage: From threat to treatment. Cells, 9:1665.

[25] Szeto, Y.T.; Wong, K.S.; Han, A.; Pak, SC. and Kalle, W. (2016): DNA protective effect of ginseng and the antagonistic effect of Chinese turnip: A supplementation study. J Intercult Ethnopharmacol,5(4):331-334.

[26] Yang, L.X.; Zhang, X. and Zhao, G. (2016): Ginsenoside Rd attenuates DNA damage by increasing expression of

DNA glycosylase endonuclease VIII-like proteins after focal cerebral ischemia. Chin Med J, 129:1955–1962.

[27] Jin, Y.; Kotakadi, V.S.; Ying, L.; Hofseth, A.B.; Cui X.; Wood P.A.; Windust, A.; Matesic, L.E.; Pena, E.A.; Chiuzan, C.; Singh, N.P, Nagarkatti, M.; Nagarkatti, P.S.; Wargovich, M.J. and Hofseth, L.J. (2008): American ginseng suppresses inflammation and DNA damage associated with mouse colitis. Carcinogenesis, 29(12):2351-9.

[28] Zhang, Y.; Li, H.; Li, B.; Jiang, S. and Jiang, L. (2014): Ginsenoside Rg3 induces DNA damage in human osteosarcoma cells and reduces MNNG-induced DNA damage and apoptosis in normal human cells. Oncol Rep, 31, 919-925.

[29] Elblehi, S.S.; Hafez, M.H. and El-Far, A.H. (2023): Panax ginseng ameliorates hepatorenal oxidative alterations induced by commercially used cypermethrin in male rats: experimental and molecular docking approaches. Environ Sci Pollut Res, 30: 109702–109723.

[30] Abdel-Azim, SH.; Hassan A.M.; Ibrahim M.I.M., Hassan N.S. and Abdel-Wahhab M.A. (2011): Potential protective effects of korean red ginseng against aflatoxins-induced oxidative stress and DNA damage in rats liver. J Food Indutr Nutr, 1(1):1-17.

[31] Cao, X.; Yao, F.; Zhang, B. and Sun, X. (2023): Mitochondrial dysfunction in heart diseases: Potential therapeutic effects of Panax ginseng. Front Pharmacol, 14: 1218803.

[32] Piaceri, I.; Rinnoci, V.; Bagnoli, S.; Failli, Y. and Sorbi, S. (2012): Mitochondria and Alzheimer's disease. J Neurol Sci, 322: 31–34.

[33] Zhang, M.; Niu, H.; Li, Q; Jiao, L.; Li, H. and Wu, W. (2023): Active compounds of Panax ginseng in the improvement of Alzheimer's disease and application of spatial metabolomics. Pharmaceuticals (Basel), 17(1):38.

[34] Wang, X.; Qi, L.; Cheng, Y.; Ji, X.; Chi, T.; Liu, P. and Zou, L. (2022): PINK1 overexpression prevents forskolin-induced tau hyperphosphorylation and oxidative stress in a rat model of Alzheimer's disease. Acta Pharmacol Sin, 43:1916–1927.

[35] Zhang, Y.; Yang, X.; Wang, S. and Song, S. (2019): Ginsenoside Rg3 Prevents cognitive impairment by improving mitochondrial dysfunction in the rat model of Alzheimer's disease. J Agric Food Chem, 67:10048–10058.

[36] Shi, Z.Y.; Zeng, J.Z. and Wong, A.S.T. (2019): Chemical structures and pharmacological profiles of ginseng saponins. Molecules, 24:2443.

[37] Szeto, Y.T.; Ko, A.W. (2013): Acute genoprotective effects on lymphocytic DNA with ginseng extract supplementation. J Aging Res Clin Pract, 2:174–7.

[38] Kim, J.Y.; Park, J.Y.; Kang, H.J.; Kim, O.Y.; Lee, J.H. (2012): Beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzyme activity, and LDL oxidation in healthy participants: A randomized, double-blind, placebo-controlled trial. Nutr J, 11:47.

[39] Trump, D.L. and Aragon-Ching, J.B. (2018): Vitamin D in prostate cancer. Asian J Androl, 20(3):244-252.

[40] Renkema, K.Y.; Alexander, R.T.; Bindels, R.J. and Hoenderop, J.G. (2008): Calcium and phosphate homeostasis: Concerted interplay of new regulators. Ann Med, 40:82–91.

[41] Zittermann A. and Gummert J.F. (2010): Nonclassical vitamin D action. Nutrients, 2:408–425.

[42] Witham, M.D.; Nadir, M.A. and Struthers, A.D. (2009): Effect of vitamin D on blood pressure: A systematic review and meta-analysis. J Hypertens, 27:1948–1954.

[43] Hart, P.H.; Gorman, S. and Finlay-Jones, J.J. (2011): Modulation of the immune system by UV radiation: More than just the effects of vitamin D? Nat Rev Immunol, 11:584–596.

[44] Vasconcelos, M.A.; Orsolin, P.C.; Oliveira, V.C.; Lima, P.M.A.P.; Naves, M.P.C.; de Morais, C.R.; Nicolau-Júnior,

N.; Bonetti, A.M. and Spanó, M.A. (2020): Modulating effect of vitamin D3 on the mutagenicity and carcinogenicity of doxorubicin in Drosophila melanogaster and in silico studies. Food Chem Toxicol, 143:111549.

[45] Nair-Shalliker, V.; Armstrong, B.K. and Fenech, M. (2012): Does vitamin D protect against DNA damage? Mutat Res, 733(1-2):50-7.

[46] Valko, M.; Izakovic, M.; Mazur, M.; Rhodes, C.J. and Telser, J. (2004): Role of oxygen radicals in DNA damage and cancer incidence. Mol Cell Biochem, 266(1-2):37-56.

[47] Wang, E.W.; Collins, A.R.; Pang, M.Y.C.; Siu, P.P.M.; Lai, C.K.Y.; Woo, J. and Benzie, I.F.F. (2016): Vitamin D and oxidation-induced DNA damage: is there a connection? Mutagenesis, 31: 655–659.

[48] Magro-Lopez, E.; Chamorro-Herrero, I. and Zambrano, A. (2022): Effects of hypocalcemic vitamin D analogs in the expression of DNA Damage induced in minilungs from hESCs: implications for lung fibrosis. Int J Mol Sci, 23(9):4921.

[49] Leyssens, C.; Verlinden, L. and Verstuyf, A. (2014): The future of vitamin D analogs. Front Physiol, 5:122.

[50] Guijarro, T.; Magro-Lopez, E.; Manso, J.; Garcia-Martinez, R.; Fernandez-Aceñero, M.J.; Liste I. and Zambrano, A. (2018): Detrimental pro-senescence effects of vitamin D on lung fibrosis. Mol Med, 24:64.

[51] Al Mahroos, M.; Yaar, M.; Phillips, T.J.; Bhawan, J. and Gilchrest, B.A. (2002): Effect of sunscreen application on UV-induced thymine dimers. Arch Dermatol, 138:1480–1485.

[52] Pawlowska, E.; Wysokinski, D. and Blasiak, J. (2016): Nucleotide excision repair and vitamin D--relevance for skin cancer therapy. Int J Mol Sci, 17(4):372.

[53] Gupta, R.; Dixon, K.M.; Deo, S.S.; Holliday, C.J.; Slater, M.; Halliday, G.M.; Reeve, V.E. and Mason, R.S. (2007): Photoprotection by 1,25 dihydroxyvitamin D3 is associated with an increase in p53 and a decrease in nitric oxide products. J Investig Dermatol, 127:707–715.

[54] Demetriou, S.K.; Ona-Vu, K.; Teichert, A.E.; Cleaver, J.E.; Bikle, D.D. and Oh, D.H. (2012): Vitamin D receptor mediates DNA repair and is UV inducible in intact epidermis but not in cultured keratinocytes. J Investig Dermatol, 132:2097–2100.

[55] Kommagani, R.; Payal, V. and Kadakia, M.P. (2007): Differential regulation of vitamin D receptor (VDR) by the p53 family: p73-dependent induction of VDR upon DNA damage. J Biol Chem, 282 :29847–54.

[56] Negri, M.; Gentile, A.; de Angelis, C; Montò, T,.; Patalano, R.; Colao, A.; Pivonello, R. and Pivonello, C. (2020): Vitamin D-induced molecular mechanisms to potentiate cancer therapy and to reverse drug-resistance in cancer cells. Nutrients, 12(6):1798.

[57] Machado, Cda S.; Venancio, V.P.; Aissa, A.F.; Hernandes, L.C.; de Mello, M.B.; Del Lama, J.E.; Marzocchi-Machado, C.M.; Bianchi, M.L. and Antunes, L.M. (2016): Vitamin D3 deficiency increases DNA damage and the oxidative burst of neutrophils in a hypertensive rat model. Mutat Res Genet Toxicol Environ Mutagen, 798-799:19-26.

[58] Pilz, S.; Tomaschitz, A.; Ritz, E. and Pieber, T.R. (2009): Vitamin D status and arterial hypertension: a systematic review. Nat Rev Cardiol, 6(10):621-30.

[59] Chatterjee, M.; Saluja, R.; Tewari, S.; Barthwal, MK.; Goel, SK. and Dikshit, M. (2009): Augmented nitric oxide generation in neutrophils: oxidative and pro-inflammatory implications in hypertension. Free Radic Res, 43(12):1195-204.

الملخص العربي

جمال شمس1 , جيهان مصطفي2 , رضا عبدالعزيز3 , اية محمد1
1 قسم الفارماكولوجيا – كلية الطب البيطري – جامعة الزقازيق – جمهورية مصر العربية
2 قسم الطب السرعي والسموم – كلية الطب البيطري – جامعة الزقازيق – جمهورية مصر العربية
3 قسم الفسيولوجي – كلية الطب البيطري – جامعة الزقازيق – جمهورية مصر العربية

يتم تعريف الاكتئاب من خلال إرتباطه باضطرابات المزاج، والتي تتكون من مجموعات من الأعراض والعلامات، تستمر من أسابيع إلى أشهر. ويؤدي إلى تغيير كبير في قدرة الشخص العادية على أداء وظائفه، ويظهر نمطًا من النوبات المتكررة. تشمل التأثيرات السامة للجينات تلف الحمض النووي الريبوزي منقوص الأكسجين (DNA) الذي يحدث في النواة والكروموسومات وبنية الحمض النووي، بما في ذلك إدخالات الحمض النووي، وتكسر الحمض النووي، والطفرات الجينية، وتشوهات الكروموسومات، وتكوين الخلايا، واختلال الصيغة الصبغية. مع تزايد انتشار استخدام الأدوية المضادة للاكتئاب في العصر الحديث، أصبح تحديد ما إذا كانت هذه الأدوية تسبب ضررًا وراثيًا أمرًا بالغ الأهمية. ينتمي سيتالوبرام، الذي يستخدم عادة في علاج الاكتئاب، إلى فئة مضادات الاكتئاب المعروفة باسم مثبطات امتصاص السيروتونين الانتقائية (SSRIs).

يستخدام الجينسنج كعلاج عشبي لسنوات عديدة. فهو يقلل من الالتهابات والجذور الحرة ويمنع الظروف أو المشكلات الصحية التي تكون مرتبطة بالعمر ، والتعب المزمن، واختلال وظائف القلب والأوعية الدموية والجهاز الهضمي. يقلل فيتامين د بشكل كبير من المؤشرات الحيوية الجهازية والأنسجة المؤيدة للأكسدة المشاركة في تطور وتطور وتكرار أمراض القلب والأوعية الدموية المزمنة والسرطان.

نظرًا للعديد من النتائج المتناقضة حول التأثيرات الضارة وسميات مثبطات استرداد السيروتونين الانتقائية (خاصة السمية الجينية)، قمنا بمراجعة التأثيرات السمية الجينية لهذه الأدوية، مع التركيز بشكل خاص على السيتالوبرام، بالإضافة إلى دراسة مراجعة عن تأثير الجينسنج وفيتامين د على تلف الحمض النووي.