Journal of Ginseng Research 47 (2023) 193–198

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: https://www.sciencedirect.com/journal/journal-of-ginseng-research

Review Article

Protective effects of Korean Red Ginseng against toxicity of endocrine-disrupting chemicals

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ARTICLE INFO

Article history:
Received 23 August 2022
Received in revised form
26 October 2022
Accepted 30 November 2022
Available online 5 December 2022

Keywords:
Endocrine-disrupting chemicals
Ginsenosides
Korean Red Ginseng
Toxicity

ABSTRACT

Several chemicals have been developed owing to the progression of industrialization, among which endocrine-disrupting chemicals (EDCs; essential for plastic production) are used as plasticizers and flame retardants. Plastics have become an essential element in modern life because they provide convenience, thus increasing EDCs exposure to humans. EDCs cause adverse effects such as deterioration of reproductive function, cancer, and neurological abnormalities by disrupting the endocrine system and hence are classified as "dangerous substances." Additionally, they are toxic to various organs but continue to be used. Therefore, it is necessary to review the contamination status of EDCs, select potentially hazardous substances for management, and monitor the safety standards. In addition, it is necessary to discover substances that can protect against EDC toxicity and conduct active research on the protective effects of these substances. According to recent research, Korean Red Ginseng (KRG) exhibits protective effects against several toxicities caused by EDCs to humans. In this review, the effects of EDCs on the human body and the role of KRG in protection against EDC toxicity are discussed.

1. Endocrine system hormones

The endocrine system plays a central role in homeostasis [1]. It maintains homeostasis by regulating hormone biomolecules and functions of the glands (such as pancreas, adrenal glands, and thyroid glands) and organs (ovaries, testes) involved in reproduction and development [2]. Hormones from the glands bind to target cells via blood, inducing signal transduction. Steroid hormones produced by the ovaries and testes are responsible for reproduction [3].

Hormones secreted by the pancreas include insulin and glucagon, which are composed of peptide bonds that mainly regulate blood sugar levels [4]. Hormones produced by the adrenal glands include epinephrine and corticoids, which are mainly involved in cardiac muscle metabolism [5]. Hormones from the thymus regulate the growth of T and B cells and are closely associated with the immune system [6]. Thyroxine and parathyroid hormones secreted by the thyroid and parathyroid glands, respectively, control the concentrations of ions, mainly calcium and phosphorus, in the blood [7]. The pituitary gland and hypothalamus secrete many hormones, mainly protein hormones with large molecular sizes. They promote water absorption as well as bone and muscle growth [8]. Abnormalities in the endocrine organs mainly affect growth and development of the reproductive organs and blood sugar levels.

2. Health benefits of ginseng

Panax ginseng Meyer (*P. ginseng*), a traditional herb cultivated in Asia, has been widely used as a herbal medicine and health supplement because of its therapeutic effects [9]. Korea red ginseng (KRG) undergoes processing, such as steaming and drying of the root of *P. ginseng*, which makes it red in color and enhances the pharmacological activity of ginseng through the chemical transformation of specific compounds called ginsenosides [10]. Ginsenosides, the bioactive ingredients of ginseng, are steroidal triterpene saponins. Owing to their structure, they can interact with extracellular/intracellular receptors and membrane-bound

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https://doi.org/10.1016/j.jgr.2022.11.007

ion channels, resulting in beneficial effects by regulating gene expression at the transcriptional level [11].

Ginsenosides have various physiological and pharmacological effects. Ginsenoside can regulate inflammatory responses by hindering the NF-κB signaling pathway or reducing the expression of cytokines and inflammation-inducing enzymes [12]. In addition, ginseng can act as an antioxidant by normalizing biomarkers related to oxidative stress. It can also promote the activity of antioxidant enzymes and decrease lipid peroxidation [13]. Ginseng may possess antimicrobial or antiviral properties that could enhance microbial resistance or suppress the expression of inflammatory cytokine genes induced by microbial infection [14,15]. Moreover, ginsenosides may regulate energy metabolism, which is related to the anti-obesogenic effect of ginseng in reducing body weight and adipogenesis in mouse models [16].

Owing to the effectiveness of ginsenosides, an increasing number of clinical studies have focused on the therapeutic and tonic action potential of ginseng. Ginseng has been widely used to prevent or treat various diseases, including diabetes, cancer, and cardiovascular diseases [17]. Patients with diabetes show abnormal metabolic conditions owing to insulin deficiency or resistance. Several studies have investigated the antidiabetic effects of ginseng, particularly in patients with type-2 diabetes with insulin resistance. In addition, ginseng can improve medicinal progress by regulating insulin secretion and antioxidant pathways [18]. With respect to its anti-cancer activity, there have been many observations that ginsenoside. It can disrupt the proliferation and migration of tumor cells *in vitro* and *in vivo* in a dose-dependent manner [19]. Ginseng can inhibit tumor growth and metastasis in breast cancer by promoting apoptotic pathways, progressing cellular senescence, and suppressing anti-inflammatory factors. Ginseng may have the potential to treat cancer and is expected to serve as an anti-tumor drug [20]. In addition, ginseng can improve cardiovascular health because its active compound can inhibit myocyte Ca^{2+} influx, which could regulate cardiac contractility [21]. In addition to Ca^{2+} modulation, ginseng can enhance nitric oxide release from vascular endothelial cells, stimulate angiogenesis, and suppress platelet aggregation, which consequently would lead to increased blood circulation and decreased blood pressure [22]. Furthermore, ginseng has remarkable efficacy in various neurological disorders, including anxiety, depression, cognitive function, and neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Impairment of synaptic plasticity causes depression symptoms; ginseng exerts antidepressant effects by increasing glutamatergic transmission and levels of monoamine neurotransmitters and promoting membrane excitability, which results in reduced depression-like behavior *in vivo* [23,24]. Neuronal death, abnormal protein aggregation, and neurofibrillary tangles are the most common pathological hallmarks of neurodegenerative diseases. Using *in vitro* and *in vivo* models of neurodegenerative diseases, researchers have reported the potential neuroprotective effects of ginseng and observed that ginsenosides can decrease abnormal protein levels, oxidative stress, and neuronal damage as well as mitigate neuroinflammation [25]. In addition, ginseng has health benefits against fatigue [26] and improves sexual arousal in premenopausal women [27].

In brief, ginseng can improve the progression and pathology of numerous diseases or symptoms as an adaptogen that helps organisms maintain optimal homeostasis against endogenous or exogenous factors (Table 1). In recent decades, ginseng has been widely used as a health supplement. Although the pharmacological mechanism underlying the beneficial effects of ginseng has not yet been clarified, researchers have selected ginseng as a therapeutic agent to prevent various diseases [17,28].

3. Endocrine-disrupting chemicals and mechanisms of actions

Endocrine-disrupting chemicals (EDCs) are harmful exogenous chemicals that interfere with the normal endocrine system in diverse animal species, including humans [30]. It causes potential dysfunctions in the environment that could affect human health [31]. EDCs mimic the original hormones in the body through hormone receptor binding, which causes health problems in the reproductive, endocrine, immune, and neurodevelopmental systems [32]. The routes of EDC exposure in humans are diverse. They are widely used in plastics, flame retardants, detergents, cosmetics, pesticides, and pharmaceuticals [33,34]. Consequently, these chemicals are absorbed into the body through the skin, oral cavity, and other parts of the body and accumulate in organs, which can cause endocrine system dysfunction, even when present in very small amounts [35]. EDC exposure during developmental periods such as pregnancy, neonatal period, and childhood can disrupt the normal development of mammals, including humans [36]. In addition, a relationship between exposure frequency or accumulation of EDCs and the occurrence of endocrine [37], neurodevelopmental, and neurodegenerative diseases exists [38]. There is scientific evidence that disease-related gene expression is induced by the disarrangement signaling process of EDCs. Due to the adverse effects, each country regulates the use of EDCs by law upon the identification of risks. However, it is difficult to define the characteristics of substances and to independently evaluate the effects of EDCs in humans. Moreover, research on diseases caused by endocrine disruptors is currently limited and is highly dependent on the dose, experimental animals, and chemical mixing ratio [33].

The mechanism of action of EDCs varies according to their structure, which is known to cause physical health problems owing to their similar actions as hormones in the human body [39]. Exposed EDCs bind to receptors of intracellular hormones, which disrupt normal biological signal transduction in the nervous and reproductive systems or homeostasis maintained by the biochemical action of hormones [40]. Endocrine disruptors may also interact with each other during biological processes and alter gene expression [41], which may result in disturbance of hormone synthesis and interference in the transportation process during signal transduction [42,43]. It adversely affects all animals, including humans. For example, EDCs such as diethylstilbestrol (DES), bisphenol-A (BPA), octylphenol, and nonylphenol bind abnormally to a receptor on a target cell, which can hinder the binding capacity of normal hormone receptors. They can non-specifically induce intercellular signaling cascades and cellular responses, such as estrogen signaling progression [44–47]. Conversely, it blocks hormone receptors and protects smooth signal transduction of hormones. An example of this is anti-androgen signaling. EDCs are structurally similar to normal androgen hormones [48]. This causes abnormal body physiology and dysregulation of signaling, which affects gene expression. Therefore, compounds exposed to the environment bind to hormone receptors and disrupt hormone homeostasis, such as estrogen, anti-estrogenic, androgenic, and anti-androgenic systems [48]. Human exposure to EDCs is characterized by complex exposure to numerous chemicals and accumulation of EDCs over time; however, mechanistic studies have not yet clarified the diverse effects of precise single or multiple exposures to EDCs on human health [49].

EDCs are toxic to various organs in the human body. Although several methods have recently been proposed to protect against the toxicity of EDCs, the best option is to avoid them. However, it is practically impossible to eliminate EDCs from modern life. Therefore, other protective measures must be established. Several studies

Table 1
Summary of beneficial effects of ginseng

Effects	Mode of activities	Ref.
Anti-inflammation	Inhibiting the NF-κB, and p38 MAPK pathway. Modulating inflammasome activation. Suppressing iNOS and COX-2 activity and PGE_2 production. Reducing expression and release of TNF-α and IL-1β.	[12,29]
Antioxidant	Reducing lipid peroxidation. Hindering the formation of malondialdehyde. Promoting the activity of SOD, GPx, GR, and CAT.	[13]
Antimicrobial, antiviral	Promoting interferon-γ secretion and NK cell activation. Repressing ERK1/2 signaling and caspase-3 activation. Inhibiting hemagglutination of microbial by polysaccharide fractions. Balancing T-helper type 1/2 immune responses upon respiratory syncytial viral infection.	[14,15]
Anti-obesity	Downregulation of expression of PPARγ, FAS, and SCD1. Promoting the AMPK pathway and GLUT4 expression in skeletal muscle. Increasing cytochrome C oxidase and fatty acid oxidation.	[16]
Anti-diabetes	Lowering G6Pase expression and glycogenolysis in the liver. Upregulating expression of GLUT1 and GLUT4 in liver and muscle. Promoting pancreatic β-cell proliferation in STZ-induced diabetic mice. Raising GLP-1 production and reducing malondialdehyde accumulation.	[18]
Anti-cancer	Activating p53 pathway in gallbladder cancer. Inhibiting expression of interferon-β and COX2. Hindering AP-1 or NF-κB mediated metastasis in carcinoma cells. Blockade of epithelial-mesenchymal transition by downregulation of HIF-1α gene in ovarian cancer.	[19,20]
Anti-cardiovascular diseases	Blocking voltage-independent Ca^{2+} channels. Enhancing proliferation of vascular endothelial muscle cells. Activating and phosphorylation of eNOS pathways. Modulating Bcl-2 and caspase level in cardiomyocytes. Activating Nrf2 pathway and increasing 6-keto-prostaglandin F1α.	[21,22]
Anti-neurological disorders	Increasing the level of 5-HT and BDNF. Blocking glucocorticoid receptor in depressed mice. Preventing cytochrome C release and inhibiting cytotoxicity. Enhancing learning and memory impairment of AD patients. Regulating neural-plasticity-related proteins in aged SAMP8 mice model.	[23–25]

NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; iNOS, inducible nitric oxide synthase; COX, cyclooxygenase; PGE_2, prostaglandin E_2; TNF-α, tumor necrosis factor-alpha; IL, interleukin; SOD, superoxide dismutase; GPx, glutathione peroxidase; GR, glutathione reductase; CAT, catalase; NK cell, natural killer cell; ERK1/2, extracellular signal-regulated protein kinase; PPARγ, peroxisome proliferator-activated receptor gamma; FAS, fatty acid synthase; SCD1, stearoyl-coenzyme A desaturase 1; AMPK, AMP-activated protein kinase; GLUT, Glucose transporter; G6Pase, Glucose-6-phosphatase; STZ, streptozotocin; GLP-1, glucagon-like peptide-1; AP-1, activator protein-1; HIF-1α, hypoxia-induced factor-1α; eNOS, endothelial nitric oxide synthase; Nrf2, nuclear factor erythroid-2-related factor 2; 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor; AD, Alzheimer's disease; SAMP8, senescence-accelerated mouse prone 8.

suggest that ginsenosides of KRG have anti-toxicity activities against EDCs because of their steroidal structure [50], which allows them to interact with cellular molecules and produce alterations at the transcriptional level or in the expression of responsible genes [51]. KRG, with an estrogen-like function, is beneficial to health because of its anti-fatigue effects and immune regulation (particularly in women); however, data on the protective activity of KRG against toxic reactions mediated by EDCs are limited.

4. Protective activities of KRG against adverse effects of EDCs

EDC exposure during development and throughout life has negative effects on human health and causes reproductive dysfunction, endocrine diseases, obesity, and neurological diseases. EDC toxicity includes induction of inflammatory responses, endocrine reticulum stress, oxidant production, cell apoptosis, adipogenesis alteration, and mitochondrial dysfunction, which results in disruption of homeostasis [52]. The evaluation of the effect of EDCs on health varies depending on the dose of the test substance, duration of exposure, and type of mixed substances. The effects of EDCs also vary according to species, sex, and age (Fig. 1).

EDCs may affect the development and progression of malignant tumors. Cell growth was significantly increased in a cancer cell model [53]. In animal models, continuous exposure to BPA also increases the occurrence of breast and prostate cancers. Similar cases have been reported in humans [54,55]. A study reported that women exposed to dichlorodiphenyltrichloroethane and polychlorinated biphenyls (PCBs) were more likely to develop breast

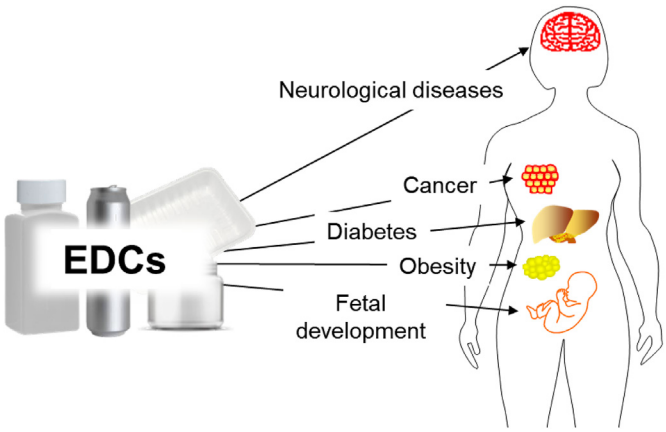

Fig. 1. Effects of endocrine-disrupting chemical exposure on human health. This image displays the main diseases caused by the impact of endocrine-disrupting chemicals on human health.

cancer than those who were not exposed [56]. In addition, there is a higher likelihood of prostate cancer in fetuses and adults exposed to EDCs such as BPA than in unexposed individuals [54].

Furthermore, substantial reports from human and animal studies indicate that exposure to EDCs causes and worsens neurological diseases. For example, exposure to dioxin-like compounds in animal models results in changes in dopamine levels

[57,58]. This suggests that there is a close relationship between endocrine disruptors and behavioral changes. EDCs that affect estrogen signaling, such as BPA and PCBs, have recently been studied for estrogen secretion, regulation, and reproductive toxicity [30,59]; however, studies on their effects on the nervous system are insufficient. In particular, their mechanisms of action in the central nervous system have not yet been systematically investigated. There are insufficient studies on neurological disorders, such as attention deficit hyperactivity disorder, which require behavioral analysis [60]. Additionally, there is a growing need for research to isolate and characterize the EDCs associated with neurological diseases. A recent epidemiological study reported attention deficit hyperactivity disorder in children born to mothers exposed to high levels of endocrine disruptors during pregnancy [61]. In addition, high levels of PCBs were detected in brain tissues [62]; therefore, endocrine disruptors may have a direct effect on development beyond the blood–brain barrier. This may be closely related to the recent increase in the incidence of neurological diseases, including Parkinson's disease [63]. Most EDCs are fat-soluble substances that can easily enter the placenta [64]. They have serious effects on normal brain development through the disruption of the signal transduction of endocrine system hormones, such as the sympathetic gland hormones of the fetus, during the brain developmental period. Learning and intellectual abilities decrease as age progresses (post adulthood), and thyroid hormones and homeostatic regulation of calcium and signaling systems in cells are affected in this process [65].

Recent research suggests a relationship between EDCs and the occurrence of diabetes [66]. Exposure to EDCs can lead to the rapid onset of metabolic syndrome [67]; however, it is difficult to exclude genetic and epigenetic effects from the onset of these metabolic diseases. Notably, metabolic disorders, including obesity, which lead to various side effects, may be associated with EDC exposure. Low- and high-dose EDC exposure causes weight gain and loss, respectively [68].

Several studies have suggested that KRG may be used to ameliorate EDC toxicity. In a recent study, BPA and malondialdehyde, a biomarker of oxidative stress, were analyzed in urine after daily administration of KRG (2.7 g) or placebo using gas chromatography/mass spectrometry and a high-performance liquid chromatography-ultraviolet detector, respectively. KRG intake reduces BPA and malondialdehyde levels and relieves menstrual irregularities, dysmenorrhea, and constipation [69]. When BPA and KRG were administered to ovariectomized mice, their effect on lipid metabolism was evaluated, indicating that KRG inhibited the increase of fatty acid levels caused by BPA [70]. Moreover, KRG significantly inhibited BPA-induced COX-2 expression, NF-κB activation, ROS generation, and A549 cell migration, suggesting that KRG may have anti-inflammatory effects on BPA-induced inflammation [71].

In addition, KRG reduces toxicity in reproductive dysfunction. When mammals, including humans, are exposed to EDCs, reproductive organ development disorders occur [72]. In a physiological study using animal models, severe destruction of the uterus, ovaries, fallopian tubes, and cervix was observed in newborn mice exposed to EDCs [73]. In addition, EDC exposure causes abnormalities in the shape of the sperm and decreases its production [74]. Similar results have been reported in humans. Typically, EDCs cause malformations of reproductive organs, decrease sperm count [75], induce tumors in the reproductive organs (including the breasts and uterus), and cause endometriosis [73,76]. For example, in the 1970s, cases were reported where the fertility of offspring born to patients treated with an anti-lactic acid drug, referred to as DES (synthetic estrogen), was reduced. DES results in uterine malformations and inhibits sperm development [77,78]. Girls born to patients treated with DES developed genital tumors, such as uterine cancer, in adulthood [79]. This supports the hypothesis that endocrine blockade affects the exposed adults and their offspring. Exposure to EDCs abnormally affects the formation and development of organs affected by sex hormones. A recent study suggested that when pregnant mice were treated with phthalates and BPA, disrupted steroidogenesis and hormonal imbalance occurred, and hormones were restored to normal levels by KRG treatment by modulating signaling pathways. Thus, KRG can alleviate the reproductive toxicity caused by phthalates and BPA as an indirect effect [80].

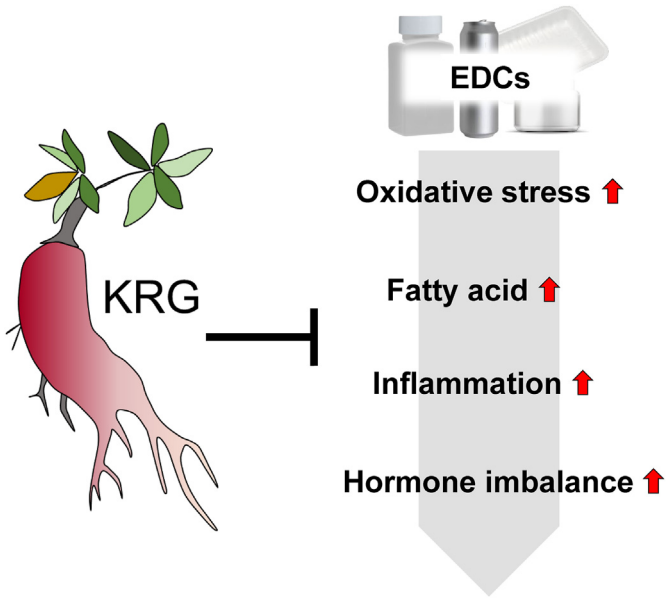

Fig. 2. Protective effects of Korean Red Ginseng against endocrine-disrupting chemical toxicity. Korean Red Ginseng inhibits oxidative stress, increases fatty acid level, inflammation, and hormone imbalance caused by endocrine-disrupting chemicals.

Collectively, EDC exposure causes ER stress, inflammatory reactions, oxidative response, obesity, and outbreaks of various diseases, and KRG can ameliorate the toxicity of EDCs through corresponding protective responses. Although there are few studies on the beneficial effects of KRG against EDC toxicity, these results suggest that KRG may be an effective therapeutic agent for EDC-induced toxicity (Fig. 2). However, further studies that consider individual variations in dose adjustment, sex, endpoints, and susceptibility to effects of the KRG treatment are needed to identify the ideal EDC-induced toxicity protection by KRG.

5. Conclusion

Owing to industrial development, human exposure to EDCs has increased in the recent years. Several studies have reported that further research on toxicity evaluation and protection through cellular and animal studies of endocrine disruptors is necessary. It is of great concern that long-term exposure to EDCs and their accumulation in the body lead to reproductive, nervous, endocrine, and behavioral disorders. In the future, the discovery of hazardous substances through the impact assessment of a single and mixed substances should be studied using various methods. In addition, further studies on drug development against the toxicity of EDCs should be conducted. KRG is considered a promising candidate to protect against EDC toxicity, and more research is needed to confirm the protective effects of KRG against EDC toxicity and implement treatment strategies involving KRG. If these

experiments are actively conducted, KRG could be used as a potential therapeutic target against the toxicity of various chemicals, including EDCs, in the near future.

Declaration of competing interest

The author declares no conflicts of interest.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1C1C100328611).

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