Protective Potential of Ginseng Root Intake Against Changes in Thyroxin (T4) Levels and Thyroid Pathophysiology of Rats Exposed to Bisphenola A (BPA)

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ARTICLE INFO

Received: June 4, 2026
Accepted: July 7, 2026
Volume: 6
Issue: 2

KEYWORDS

Ginseng root, bisphenol A, oxidative stress, thyroxine

Endocine disrupting chemicals (EDCs) are chemicals that can affect the endocrine gland system. Bisphenol A (BPA) acts as an EDC for thyroid gland function. A study was conducted to determine the protective potential of ginseng root against BPA toxicity on changes in thyroxine levels and thyroid pathophysiology in male rats. This experimental study used a Completely Randomized Design (CRD) with 24 rats, four treatments and six replications. Each treatment consisted of control/no treatment (P0), administration of 54 mg/kg ginseng root (P1), administration of 50 mg/kg BPA (P2) and administration of 54 mg/kg ginseng root and 50 mg/kg BPA (P3). Ginseng root and BPA were administered orally by gavage for four weeks. Rats were euthanized on the 29nd day for blood sampling and thyroid organ removal. The results showed a significant difference ($P<0.05$) between the control and the group given ginseng root and exposed to BPA on thyroxine levels and pathophysiology of male rats. This study concluded that administering ginseng root can increase thyroxine hormone levels and improve thyroid physiology in rats exposed to BPA.

1. Introduction

Repeated exposure to chemicals, through everyday products, from cooking utensils to food and beverage packaging, has the potential to disrupt endocrine function. Endocrine-disrupting chemicals (EDCs) are single or mixed substances originating from outside the body that alter hormone homeostasis in the endocrine system and cause a decline in an organism's health. Hormone-disrupting compounds have the potential to alter cell and tissue behavior in both the short and long term. Humans are exposed to EDCs through ingestion or oral intake of food and water (Fuhrman et al., 2015).

We can find many environmental chemicals and are known to disrupt endocrine function, one of which is BPA. Bisphenol A (BPA) is an organic synthetic compound used as an additive in the production of polycarbonate plastic and epoxy resin. Bisphenol A with the chemical name 4,4'-(1-methylethylidene) is the basic material of the polycarbonate plastic industry which is widely used in household appliances, food packaging, mineral water bottles, bottles and baby food containers. Epoxy resin is used as a wall coating material in canned food and beverage packaging. (Moller et al., 2012). The results of studies show the presence of very high levels of BPA in canned food (Chen et al., 2016). BPA residues are found in surface waters, in fish tissue and can transfer from cans to food and from baby bottles to milk (Wisniewski et al., 2015).

Bisphenol A, a source of EDCs, can cause various health problems, including disrupting the biosynthesis, transport, and biosynthesis of thyroid hormones (Bansal and Zoeller, 2019). Thyroid hormones have broad functions in development and physiological functions, including many aspects of metabolism. Thyroid hormones, namely 3,3',5-triiodo-L-thyronine (triiodothyronine, T3) and 3,3',5,5'-tetraiodo-L-thyronine (thyroxine, T4), are produced by the thyroid gland through an iodination reaction that occurs in the thyroglobulin molecule located in the thyroid. Under the influence of thyroid-stimulating hormone (TSH, or thyrotropin), T4 and T3 are secreted from thyroid follicular cells into the circulation (Gereben et al. 2008; Ma et al. 2009). Changes in circulating thyroid hormone levels can cause pathologies (hypothyroidism and hyperthyroidism).

Ginseng root is a traditional herb cultivated as a herbal medicine and health supplement due to its therapeutic effects. Ginsenosides, a specific compound found in ginseng, have various physiological and pharmacological effects. Ginsenosides can regulate the inflammatory response by inhibiting the NF-kB signaling pathway or reducing the expression of inflammatory cytokines and enzymes. Furthermore, ginseng can act as an antioxidant by normalizing biomarkers associated with oxidative stress. It can also increase the activity of antioxidant enzymes and reduce lipid peroxidation (Kim et al., 2017).

Measuring thyroid hormone concentrations in animals can provide useful information for assessing thyroid function and understanding the impact of environmental chemicals on normal thyroid hormone metabolism in humans. Studies on thyroxine (T4) levels in rats fed ginseng root and exposed to bisphenol A have been limited and have limited references. Therefore, this study aimed to determine the protective potential of ginseng root intake against changes in thyroxine (T4) levels and thyroid pathophysiology in rats exposed to bisphenol A (BPA).

2. Material and Methods

2.1 Materials

This study has obtained an Animal Ethics Approval Certificate with Number: B/176/UN14.2.9/PT.01.04/2024). The experimental animals used in this study were male rats, 3 months old with a body weight of 150-200 g. The experimental animals were placed in four cages randomly. Each

cage contained 6 mice that were acclimatized for 7 days and given food in the form of chicken pellets and tap water. Feeding and drinking were carried out ad libitum. The ginseng root used was a local herbal herbal panax ginseng powder capsule and each capsule contained 600 mg of ginseng root powder. The dosage determination was based on the conversion rate from human (70 kg) to rat (200 g) which was 0.018 x 600 = 10.8 mg/200 g BW = 54 mg/kg BW. The bisphenol used was produced by Loba Cheme PVT, LTD. The amount of BPA used was 50 mg/kg BW (El Morsy and Ahmed, 2020).

2.2. Experimental Design

This experimental study used a Completely Randomized Design (CRD) and consisted of four treatments and six replications. Each treatment consisted of a control/no treatment (P0), administration of 54 mg/kg ginseng root (P1), administration of 50 mg/kg BPA (P2), and administration of 54 mg/kg ginseng root and 50 mg/kg BPA (P3). The ginseng root and BPA were administered orally by gavage for four weeks (28 days).

2.3. Thyroxine Level Measurement

One day after the end of treatment, namely the 29th day, samples were taken with the following steps: rats were euthanized by intraperitoneal anesthesia using ketamine at a dose of 80-100 mg/kg and xylazine at a dose of 10 mg/kg (Levin-Arama et al., 2016). Blood samples were taken directly from the heart with a 5 mL syringe and collected in an anticoagulant tube. Plasma was obtained by centrifuging the blood sample for 10 minutes at 3000 r.p.m. Plasma was stored at -20˚ C until used for hormone testing (Aboubaker, 2021). Determination of thyroxine hormone levels used the Rat Thyroxine ELISA Kit, T4 Catalog No.: EA0027Ra. The kit is manufactured by Bioassay Technology Laboratory (BT LAB), Shanghai Korain Biotech Co Ltd.

2.4. Thyroid Preparation

The blood samples from the mice were then dissected. The thyroid organs were removed and then cleaned in a 0.9% NaCl solution. Thyroid structure was observed using paraffin-embedded slides and H-E staining. The removed organs were then placed in small vials filled with 10% Neutral Buffered Formalin (NBF) for fixation, dehydration, embedding, blocking, sectioning, staining, and covering (Kiernan, 2015).

2.5. Data Analysis

The collected data consisted of qualitative and quantitative data. The qualitative data were analyzed descriptively and presented in microphotograph form. The quantitative data were analyzed using ANOVA and further tested using Duncan's test at a 0.05% level of accuracy.

3. Result and Discussion

3.1 Result

The average results of thyroxine hormone levels in rats given ginseng root and exposed to BPA can be seen in Table 1.

Table 1. Results of average thyroxine levels in rats given ginseng root and exposed to BPA

Treatment	Thyroxine levels (ng/mL)
	Means ± SD
P0	56,97±0,37[a]
P1	57,69±1,73[a]
P2	42,13±1,30[b]
P3	55,31±1,59[a]

Description: Different letters in the same column indicate significantly different values ($P<0.05$). Control/no treatment (P0), administration of 54 mg/kg ginseng root (P1), administration of 50 mg/kg BPA (P2), and administration of 54 mg/kg ginseng root and 50 mg/kg BPA (P3).

Based on the results of statistical analysis in Table 1, it shows that the administration of treatment (P1, P2, and P3) had a significant effect ($P<0.05$) on the levels of the thyroxine hormone in rats. In the control/untreated group (P0), there was no significant difference ($P>0.05$) between the P1 group (administration of ginseng root 54 mg/kg) and the P3 group (administration of ginseng root 54 mg/kg + BPA 50 mg/kg). This shows that the administration of ginseng root (P1) and the control (P0) had the same effect on thyroxine hormone levels. Although the average value of hormone levels in P1 showed a slight increase compared to the control (P0), the P3 group showed results close to the control (P0). In the control (P0) group, there was a significant difference ($P<0.05$) with the P2 group. This shows that the administration of BPA can reduce the thyroxine levels in rats. In the P2 group, the thyroxine level was 42.13 ng/mL. The average decrease reached 26.10% from the control group (P0).

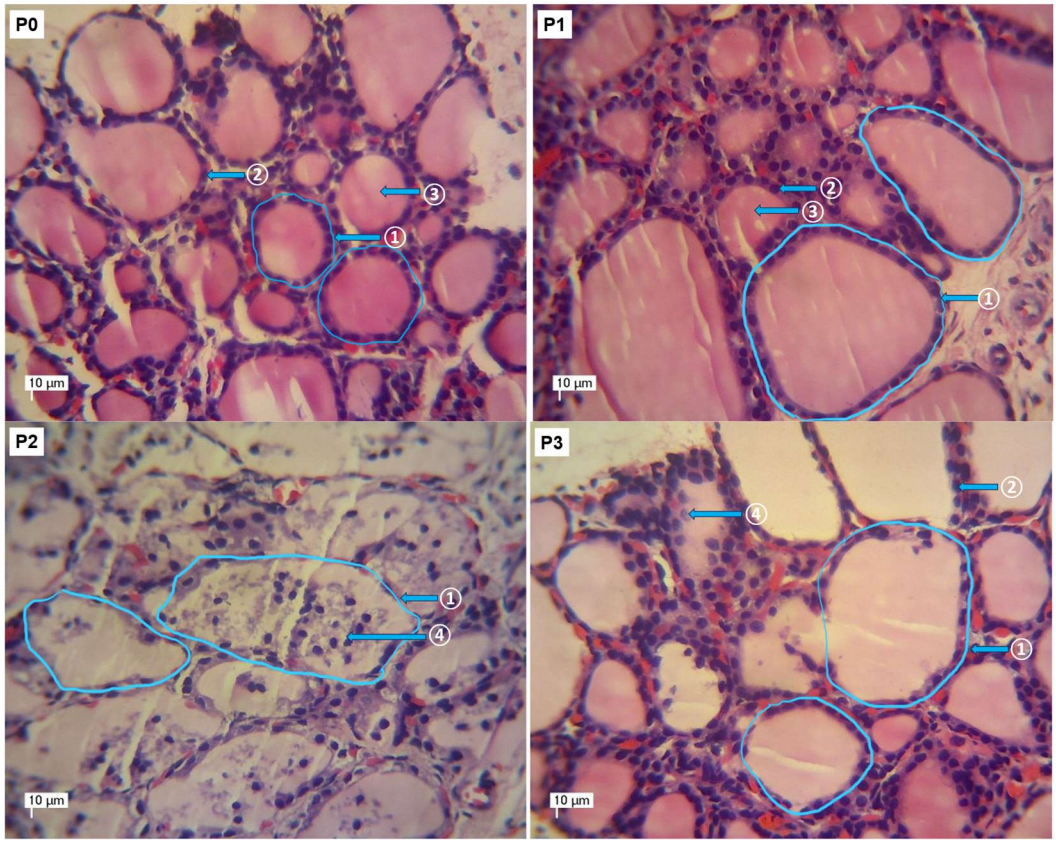

Figure 1. Microscopic structure of the thyroid pathophysiology of rats
Description: Control/no treatment (P0), ginseng root 54 mg/kg (P1), BPA 50 mg/kg (P2), and ginseng root 54 mg/kg and BPA 50 mg/kg (P3). ①Follicles, ② Epithelial cells, ③ Colloid, ④Exfoliated cells, and clear follicle lumen. (400x, HE)

Figure 1 shows the microscopic structure of the thyroid pathophysiology of male rats after being given ginseng root and BPA. In the control (P0), the microscopic structure of the rat thyroid is normal. The thyroid structure consists of follicles surrounded by cuboidal epithelial cells with pink colloid. In the group given ginseng root 54 mg/kg (P1), the rat thyroid structure was normal (the same as the P0 group). In the group given BPA (P2), the thyroid structure was abnormal. The thyroid structure showed epithelial cells released into the follicle lumen and the lumen appeared clear. The group given ginseng root 54 mg/kg and BPA 50 mg/kg (P3) showed a structure that could return to normal, although there were still cells released into the follicle lumen.

The thyroid gland, located on the side of the trachea, secretes two types of hormones: thyroxine (tetraiodothyronine) or T4 and triiodothyronine or T3. The biosynthesis of T4 (80%) and T3 (20%) is controlled by a hormone secreted by the pituitary gland, thyroid-stimulating hormone (TSH). TSH secretion is under the control of the hypothalamus, which secretes Thyroid-Releasing Hormone (TRH). These hormones play an important role in regulating body metabolism, the function of various organs, and maintaining overall body health (Braun and Schweizer, 2018). Thyroid-disrupting compounds (EDCs) can include various synthetic chemicals or industrial byproducts, pesticides, heavy metals, and bioactive compounds that can disrupt the hypothalamic-pituitary-thyroid axis, biosynthesis, secretion, transport, metabolism, and local action of thyroid hormones (Olievera et al., 2019).

This study showed a decrease in thyroxine (T4) levels in the group given BPA. The decreased thyroxine levels are due to BPA's chemical structure being similar to thyroxine. According to Kim and Park (2019), BPA has a chemical structure similar to thyroxine and can easily bind to thyroid receptors (TRs) and mimic the mechanism of action of thyroid hormones. Bisphenol A, which binds to TRs, has the potential to inhibit T4 binding and disrupt the normal function of the thyroid hormone system. This can lead to disruptions in various physiological processes in the body. Gorini *et al.* (2020) stated that BPA binding to TRs, particularly TRα1 and TRβ1, can affect thyroid gene expression. Hu *et al.* (2023) reported that BPA and its analogs can reduce the expression of TSHRH, TG (Thyroglobulin), NIS (Sodium Iodide Symporter), and TPO in vivo. Thyroglobulin (TG) is known to function as a protein substrate for iodination (Citterio *et al*., 2019). Thyroglobulin is synthesized by thyroid gland thyrocytes and is a large glycoprotein that acts as a precursor of thyroid hormones (T3 and T4). The inhibitory effect of BPA on TG has the potential to cause insufficient iodide supply and inhibit thyroid hormone synthesis (Hu *et al*., 2023).

Iodide is an essential element in the biosynthesis of the thyroxine hormone, and low iodide levels can cause disorders in the body. This is supported by several authors. Thyroglobulin is a precursor of T4 and T3, both hormones produced by thyroid follicular cells before being secreted and stored in the follicle lumen. Thyroid hormone production depends on the availability of iodide. Iodide deficiency can disrupt thyroid hormone synthesis, which can lead to conditions such as thyroid enlargement (goiter) and hypothyroidism (Knobel, 2016). BPA interferes with the expression of genes and proteins involved in thyroid synthesis, such as Slc5a5, which encodes NIS and TPO, resulting in decreased thyroid hormone synthesis (hypothyroidism) (Wu et al., 2016; Silva et al., 2018).

Iodide is actively absorbed from the bloodstream through the NIS process. Sodium Iodide Symporter (NIS) is a membrane glycoprotein protein that actively transports sodium (Na+) and iodide (I-) ions into thyroid follicular cells. This mechanism is the first step in thyroid hormone synthesis. BPA exposure can reduce iodide uptake in FRTL5 cells and TPO activity in isolated rat thyroid microsomes (Wu et al., 2016). The enzyme thyroid peroxidase (TPO) helps convert iodine into thyroid hormones (T3 and T4). In female rats, BPA exposure decreases thyroid iodide uptake and TPO activity (Silva et al., 2018). These findings suggest that BPA can inhibit thyroid hormone synthesis. BPA administration can reduce T4 levels in people aged ≥20 years using urine samples (Meeker et al., 2011). BPA exposure can reduce serum T4 levels in people aged 18–94 years (Sriprapradang et al., 2013).

Furthermore, the low thyroxine levels in the BPA-treated group were likely caused by impaired thyroid hormone transport. Thyroid hormones circulating in the bloodstream bind to thyroid-binding globulin (TBG) and transthyretin (TTR). BPA can bind to TTR (Cao et al., 2011). Competitive binding to thyroid hormone transporter proteins can disrupt thyroid hormone transport. Dong and Wade (2017) reported that BPA can inhibit thyroid hormone uptake through the monocarboxylate thyroid hormone transporter 8 (MCT8) in the brain. Monocarboxylate thyroid hormone transporter 8 (MCT8) is a highly active and selective protein for transporting thyroid hormones (T3 and T4) into and out of cells. This protein is important for brain development because it acts as a channel for thyroid hormones across the blood-brain barrier. MCT8 dysfunction can reduce thyroid hormone sensitivity in the hypothalamus and pituitary gland, leading to central hypothyroidism, and increase T3 in peripheral tissues, leading to peripheral hyperthyroidism. Zhou et al. (2017) stated that BPA can increase the incidence of thyroid cancer and nodular goiter.

Thyroid pathophysiology is studied because thyroid gland activity can be determined from the mechanisms of its dysfunction and from structural abnormalities. The thyroid structure

consists of follicles with cuboidal epithelial cells, which contain colloid (Albasri et al., 2014). A normal thyroid structure can perform its function in synthesizing thyroid hormones (T3 and T4). In this study, epithelial cells were found to be shed into the follicle lumen (desquamation), and the follicle lumen appeared empty/clear, indicating the absence of colloid (Figure 1). Thyroid epithelial cells (thyrocytes) can shed into the lumen of the thyroid follicle. Desquamated cells that shed from the basal layer of the follicle can be either normal or pathological. Rajab et al. (2015) reported that this partial shedding process is a normal part of thyroid gland function, especially during the involution of hyperplastic glands. In a healthy thyroid gland, cells are continuously replaced and shed. This process ensures the gland maintains its structure and function. Shedding is thought to be the gland's way of removing excess membrane material added during the active phase. However, this study found excessive shedding in the lumen of the thyroid follicles. Thyroid epithelial cells are known to synthesize the hormone thyroxine (Albasri et al., 2014). If all the epithelial cells of the thyroid follicles were shed from the basement membrane simultaneously, the follicles would lose their structural and functional integrity. Thyroid follicles are the structural and functional units of the thyroid gland (Lee et al., 2016). Follicles that lose their structural integrity cannot form a colloid space to store thyroid hormones and will lose their functional capacity to produce and release thyroid hormones. An empty/clear follicle lumen that does not store colloid indicates a dysfunctional thyroid gland and can lead to disease. This is consistent with other authors who reported that follicles with reduced intraluminal colloid can cause thyroid gland enlargement (goiter), a disease condition in which the thyroid follicular cells that continue to produce colloid experience decreased function due to iodine deficiency, resulting in swelling of the thyroid gland (Albasari et al., 2014; Qureshi et al., 2015).

BPA exposure is potentially harmful to health because it can increase the production of reactive oxygen species (ROS). Reactive oxygen species (ROS) are molecules and atoms with unpaired electrons, known as free radicals. Antioxidants are reducing agents that can neutralize free radicals, thereby preventing oxidation reactions (Amjad et al., 2020). People who consume ginseng root can protect the thyroid from toxicity caused by BPA exposure, so ginseng root is an antioxidant that can protect the body's cells from excess free radicals. This can be explained by the antioxidant mechanism to fight ROS. The body's endogenous antioxidants are primarily responsible for eliminating excess ROS by preventing lipid peroxidation by endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), or the glutathione (GSH) system. This endogenous antioxidant is able to regulate free radical reactions and restore cell integrity (He et al., 2017). Ginseng root can protect the thyroid from BPA toxicity due to the presence of ginsenosides. Ginsenosides are the main active compounds in ginseng and are considered powerful antioxidants that reduce oxidative stress (Saw et al., 2012). This is consistent with the results of research by Jung et al. (2022), which reported that ginseng administration can repair thyroid damage caused by BPA exposure. Thus, detection of thyroid disorders can be identified from thyroxine levels and the microscopic structure of the thyroid. Ginseng root, which functions as an antioxidant, can protect the thyroid from the adverse effects of BPA. This has implications for the public that ginseng root can be used as a natural ingredient to reduce the negative impacts of BPA exposure for a healthier life.

4. Conclusion

Administration of ginseng root maintained thyroxine levels within the normal range and provided protection and prevented thyroid dysfunction in rats exposed to BPA.

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