TRENDS IN SCIENCES 2025; 22(10): 10531
https://doi.org/10.48048/tis.2025.10531 RESEARCH ARTICLE

Effects of Several Polyphenols on Some Hematological and Weight Parameters in Rats with Experimental Hypothyroidism

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Received: 1 May 2025, Revised: 1 June 2025, Accepted: 8 June 2025, Published: 15 July 2025

Abstract

Deficiency of thyroid hormones in the blood is described as hypothyroidism. Long-term usage of drugs for the treatment of hypothyroidism can lead to serious adverse effects, for example, tachycardia, nervousness, anxiety, tremors, excessive sweating and symptoms can often recur when medication is stopped. For this reason, it is important to find new harmless, natural compounds in the treatment of hypothyroidism. This study was carried out to study the time a rat can find its way in a special labyrinth in thyroid hypothyroidism, the number of erythrocytes, leukocytes in blood, the rate of agglutination of erythrocytes and the total weight of the rat and the weight of the thyroid gland, thymus, spleen, adrenal gland, and studying the effects on it of the sum of polyphenols which separated 9 plants. Adult male rats were housed in standard cages, and hypothyroidism was induced by intragastric administration of mercazolil at a dose of 1.2 mg/ 100 gr of body weight for 21 days. On day 22 of the experiment, physiological indicators of both the healthy control and hypothyroid groups were assessed. Starting from that day, plant polyphenols were administered to the hypothyroid group with a special intragastric probe at a dose of 10 mg/kg/day for 7 days (6 rats per group, 9 groups in total). In summary, plant polyphenols included *geranium sanguineum, vitis vinifera, atraphaxis pyrifolia, pistacia vera, rhus glabra* plant polyphenols with a corrective effect on more parameters among the 9 polyphenols. Further research is also currently underway to confirm this information.

Keywords: Adrenal glands, Cognitive function, Erythrocyte, Glucose, Leucocyte, Spleen, Thyroid gland, Thymus

Introduction

Endocrine diseases are very common in Asia, and thyroid diseases occupy one of the leading places among them. Especially, in recent years, the prevalence of thyroid diseases has been rising to alarming levels. For this reason, it is important to identify new harmless natural compounds that prevent and treat thyroid diseases and various pathological conditions caused by them. In this regard, the approach to the use of biologically active substances separated from plants for the treatment of thyroid dysfunction is becoming more widespread around the world. Because they are effective, safe, and have fewer side effects. Plants have several secondary metabolites such as phenols, phenolic acids, flavonoids, alkaloids, tannins, quinones, coumarins, saponins, terpenoids, triterpenoids, glycosides, and organic acids [1], which are compounds with high biological activity. The aim of this study is to study the effect of the polyphenols isolated from several plants on certain conditions that occur in hypothyroidism of the thyroid gland. Polyphenols are very important secondary metabolites of plants. Until now, there are about 8000 polyphenolic structures found and described in plants [2]. Polyphenols are a large group of compounds containing phenolic acids, flavonoids (flavonols, flavanones, flavan-3-ols, flavones, anthocyanins, and isoflavones), lignans, stilbenes, and, according to some classifications, tannins and coumarins [3,4]. Polyphenols are an important component of plant-derived food that has a beneficial effect on human health. Polyphenols are responsible for the antioxidant, antithrombotic, and anti-inflammatory properties of several metabolic syndromes (type 2 diabetes mellitus, obesity, systemic hypertension and atherogenic dyslipidemia) [5,6] also prevent or reduce the symptoms of cardiovascular disease (atherosclerosis, myocardial infarction, heart failure, and stroke [6,7]. In addition, polyphenols with their many functional groups, double bonds, and aromatic rings have an ideal structure to function as an effective antioxidant [8]. For this reason, they can prevent the initiation of free radical reactions of peroxidation of lipids, oxidation of proteins and carbohydrates, and oxidative damage of nucleic acids [2]. For many years, polyphenols have been of great interest, especially because of their antioxidant properties, which are used in the prevention and treatment of many diseases. Unfortunately, as with any chemical, polyphenols can have a detrimental effect, depending on the conditions, dosage, and interaction with the environment. In particular, polyphenols such as flavonoids are known to have negative or beneficial effects on thyroid function. Consumption of certain flavonoids can lead to hypothyroidism, especially in areas with low iodine levels. Some flavonoids can affect the synthesis of thyroid hormones, their effect on target tissues, and their metabolism [9]. According to the recent data, natural compounds such as resveratrol, catechins, curcumin, myricetin, quercetin, and apigenin may be useful in the treatment of thyroid cancer by slowing or blocking development [10]. Taking into account the beneficial and harmful effects of polyphenol compounds on the thyroid gland, it was aimed to study the range of effects of polyphenol compounds isolated from several plants on certain parameters of the body in the context of experimental hypothyroidism, and during the experiment, the following polyphenols were used.

Getasan is isolated from plant raw materials - the above-ground part of geranium sanguineum (*Geraniaceae*). The main substances are hydrolyzable tannins (bihexahydroxydiphenoyl-trigalloyl-glucose, 1,3-bis-O-digalloyl-2-O-galloyl-4,6-hexahydroxy diphenoyl-β-D-glucose, 1,2,3-tri-O-galloyl-4,6-hexahydroxidiphenoyl-β-D-glucose, 2-O-galloyl-β-D-glucose, 2,3-di-O-galloyl-β-D-glucose, 3-O-galloyl-β-D-glucose, quercetin, kaempferol, gallic acid, rutin).

Providin is a composition of tannins isolated from the sum of the polyphenols of the seeds of various cultivated grape varieties - *Vitis vinifera L.* family *Vitaceae*, native to the Republic of Uzbekistan. The main substances are catechins and proanthocyanidins (Proanthocyanidin-1, (+)-catechin, (±)-gallocatechin, (-)-epicatechin, (-)-epicatechingallat, proanthocyanidin-2, chrysantemin, delfinidin, oenin, malvin, kallistefin, pelargonin).

Rutan is the sum of polyphenols. It is isolated from the leaves of *rhus coriaria* (*Anacardiaceae*), whose plantations are established in the Republic of Uzbekistan. The main substances are hydrolyzable tannins (3,6-bis-O-digalloyl-1,2,4-tri-O-galloyl-β-D-glucose, Rutin, 2,3-di-O-galloyl-β-D-glucose, 2-O-galloyl-β-Dglucose, 3-O-galloyl-β-D-glucose, 6-O-galloyl-β-D-glucose, 1,4,6-tri-O-galloyl-β-D-glucose, 1,2,3,4,6-penta-O-galloyl-β-D-glucose, quercetin, kaempferol, gallic acid).

Atraphaxis pyrifolia- Curly pear-leaved, family. *Polygonaceae*. The sum of polyphenols is isolated from the leaves of Atraphaxis pyrifolia. The composition of polyphenols contains flavonols: Quercetin, kaempferol kaempferol, quercetin and myricetin, tanins, catechins.

Euphorbin is the sum of polyphenols isolated from the roots of the plant *Euphorbia ferganensis* B.Fedtch. family. *Euphorbiaceae*, native to the foothills of the Fergana Valley. The main substances are gallo- and ellagotannins (HHDP-6-(O-β-D-glucopyranosido)-2-(O-1-O-trigalloyl-β-D-glucopyranose), 1-O-galloyl-2,4-valoneoyl-3,6-hexahydroxydiphenoyl-β-D-glucose, 3-O-galloyl-1,2-valoneoyl-β-D-glucose, 2-O-galloyl-4,6-valoneoyl-β-D-glucose, 1,2-di-O-galloyl -4,6-valoneoyl-β-D-glucose, 1,2-di-O-galloyl -3,6-valoneoyl-β-D-glucose, 1-O-bisgalloyl-2,4-valoneoyl-β-D-glucose, 1,3-dihydrodigalloyl-4-valoneat- β-D-glucose).

Acer semenovii- Semenov maple, family *Aceraceae* Juss. The sum of polyphenols from the leaves of Acer semenovii. The main substances are flavonoids and tannins (quercetin- 3-O-glucoside, rutin, quercetin, kaempferol, (+)-catechin, (-)-epicatechin, gallic acid, (-)-epicatechingallat, 2-O-galloyl-β-D-glucose, Proanthocyanidin, ellagic acid, apigenin-6-C-glucoside, 1,6- bis-O-galloyl-β-D-glucose, isoquercetin).

Anacardin-1,2 (ANK) is the sum of polyphenols from the leaves of *Pistacia vera*, sem. *Anacardiaceae*. The main substances are gallotannins (pentagalloylglucose, hexagalloyl-glucoside, heptagalloyl-glucose, oktagalloyl-glucose, nonagalloyl glucose, (+)-catechin, gallic acid 3-O-gallate).

The sum of polyphenols from the leaves of *Rhus glabra*, sem. *Anacardiaceae*. The main substances are gallotannins (1,2,3-tri-O-galloyl-4,6-hexahydroxidiphenoyl-β-D-glucose, 1,2,3,4-tetra-O-galloyl-β-D-glucose, 1,2,3,4,6- 1,2,3,4,6-penta-O-galloyl-β-D-glucose, 2-O-galloyl-β-D-glucose, 2,3-di-O-galloyl-β-D-glucose, 3-O-galloyl-β-D-glucose, quercetin, kaempferol, gallic acid, quercetin-glucoside). It was hypothesized that due to the high biologically active compounds contained in the given plants, the thyroid gland can have a positive effect on certain blood parameters as well as weight indicators in hypothyroidism.

The thyroid gland and its hormones are important in the homeostatic regulation of key physiological mechanisms such as organ development, body growth, and energy expenditure in all vertebrates [11]. Thyroid hormone affects the system of almost all organs in the body, including the heart, central nervous system, autonomic nervous system, musculoskeletal system, digestive system, and general metabolism. In general, thyroid hormones, when bound to nuclear receptors, activate genes to increase metabolic rate and thermogenesis [12]. Thyroid hormones affect many aspects of cell physiology, such as cell growth, differentiation, and apoptosis, and the cell is the main regulator of energy metabolism and thermogenesis. These hormones increase oxygen consumption and heat production. The biological effects of thyroid hormones (T_3 and T_4) are mediated by the interaction of T_3, a biologically active hormone, with the nuclear receptor of thyroid hormones (TH), which determines whether or not T_3 enhances target gene expression [11,13]. Experimental studies show that several processes associated with thyroid hormones help regulate metabolic homeostasis in humans [14]. The nuclear and non-genomic effects of these hormones affect key metabolic pathways that control energy balance by regulating energy expenditure and accumulation through central and peripheral movements [15]. Modulates appetite and food intake and regulates body weight [16]. In children, thyroid hormones have synergistic effects with growth hormone to stimulate bone growth. Chondrocytes, osteoblasts and osteoclasts are induced in this. Thyroid hormone also promotes brain maturation through axonal growth and myelin sheath formation [17]. In the case of hypothyroidism of the thyroid gland, however, there is a decrease in the above functions of hormones [18]. Hypothyroidism, caused by decreased thyroid hormone activity, usually manifests as bradycardia, cold intolerance, constipation, fatigue and weight gain, decreased attention, depression, diffuse muscle pain, and menstrual cycle disorders, dry skin, thinning and loss of hair [12]. Overall reduced basal metabolic rate may manifest as apathy, dry skin, increased low-density lipoproteins, and increased triglycerides. Hypothyroidism can lower sympathetic activity, leading to sweating, bradycardia, and constipation.

Materials and methods

The experiments were carried out in the laboratory of the Department of Human and Animal of the National University of Uzbekistan. The experiments were conducted on 66 healthy adult male rats weighing between 180 and 220 g. The animals were randomly divided into 11 groups (randomization helps to minimize pre-existing differences between groups). Each group consisted of 6 rats (n = 6). Group 1 served as the intact (untreated) control group, while experimental hypothyroidism was induced in all remaining groups. To induce the hypothyroidism model, mercazolil was administered to the stomach in a peroral manner for 21 days at a dose of 1.2 mg/100 gr through a special probe [19,20]. This drug has an antithyroid effect and blocks the enzyme peroxidase, which provides the iodination of the amino acid tyrosine as triiode and tetraiodothyronine. The result is a decrease in the synthesis of thyroid hormones [21]. Rats of the hypothyroidism group were fed a standard diet during the induction of disease in the same way as rats in a healthy group. On the 22nd day of the experiment, a special maze of size 45×90×10 cm^3 was placed to test the cognitive functions of healthy and hypothyroidism group rats, and the time to reach the food was determined. Then, the weight was examined and decapitated, and the number of erythrocytes and leukocytes in the blood was counted on the 10× objective of the microscope using the Goryayev chamber. The rate of agglutination of erythrocytes was accomplished using the phytogemoagglutination method, and the number of non-agglutinated erythrocytes was determined using the Goryayev chamber on the 10× objective of the microscope [22,23]. Then the weight of the thyroid gland, thymus gland, the spleen and the adrenal glands of the hypothyroid rat model were determined and compared with healthy and hypothyroid rats. The rats in the remaining hypothyroidism group, however, were classified into 9 groups and corrective work was carried out using polyphenols isolated from plants. Group 1 getasan (*g.sanguineum*) (n = 6), group 2 providin (*v.vinifera*) (n = 6), group 3 rutan (*r.coriaria*) (n = 6), group 4 *atraphaxis pyrifolia* (n = 6), group 5 *acer semennovii* (n = 6), group 6 euforbin (*e.ferganensis*) (n = 6), group 7 anacardine 1 (ANK 1) (*p.vera*) (n = 6), group 8 anacardine 2 (ANK 2) (*p.vera*) (n = 6), group 9 polyphenols of *r.glabra* (n = 6) were sent to rats intragastrically of the experimental hypothyroidism model at a dose of 10 mg/kg for 7 days. After 7 days, the cognitive functions of rats of all groups in the labyrinth, the content of blood, the number of erythrocytes and leukocytes, the rate of agglutination of erythrocytes, the total mass, and the weight of the thyroid, thymus gland, spleen and adrenal glands were measured. The results obtained were compared with those in the hypothyroidism group. The targeted results were statistically processed using the parametric method of comparing the average values (M ± m) of control and experimental values, and the degree of reliability was assessed by the t-criterion of Student. The graphics were created through the origin 8.6 program.

Results and discussion

The relationship of cognitive function and glucose in experimental hypothyroidism.

Phytochemicals are naturally biologically active compounds, and according to experimental and epidemiological studies, they contain several biologically active compounds that have beneficial properties for the body. Recent research suggests that some phytochemicals, such as most polyphenols, have neuroprotective effects [24]. Therefore, in these studies, the neuroprotective effects of several plant polyphenols on cognitive disorders caused by hypothyroidism in laboratory rats was studied. On the 22nd day of the experiment, rats were examined by placing them in a special maze (**Figure 1**) in order to check their cognitive characteristics.

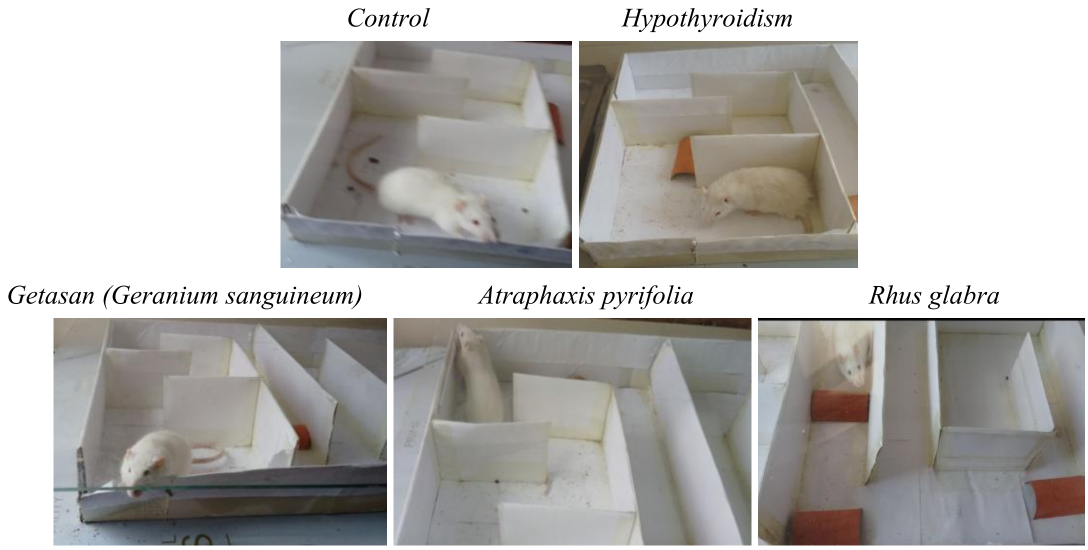


Figure 1 The movement of experimental rats in the labyrinth (the polyphenols that gave the best results were described as rats in groups).

In this case, when hypothyroid rats were compared to healthy ones, the average time taken to find a path in a maze was 3.355 ± 0.44 min in the healthy group, whereas it was 5.33 ± 0.43 min in the hypothyroid group - a 59% increase compared to the healthy group, which was statistically significant ($p \leq 0.01$). After that, for 7 days, the sum of polyphenols isolated from several plants was lowered perorally into the stomach. According to the results, rats given polyphenols from the *g.sanguineum* plant were found there was a 3.19 ± 0.44 min and it was 40% reduction in time to be able to find a path ($p \leq 0.01$) compared to rats in the hypothyroidism. Group, the sum of *v.vinifera* polyphenols is 29% ($p \geq 0.05$), *r.coriaria* polyphenols sum to 38% ($p \leq 0.01$), the group of rats for which *a.pyrifolia* plant polyphenols have been given is 35% ($p \leq 0.01$), with the polyphenols of *a.semennovii* are 32% ($p \geq 0.05$), *e. ferganensis* polyphenols by 31% ($p \geq 0.05$), *p.vera* anacardin 1 and anacardin 2 polyphenols by 25%, a group of rats given *r.glabra* plant polyphenols were found to have a 33% decrease in time to find a path in the maze ($p \leq 0.01$) to compare with the hypothyroidism (**Figure 2**).

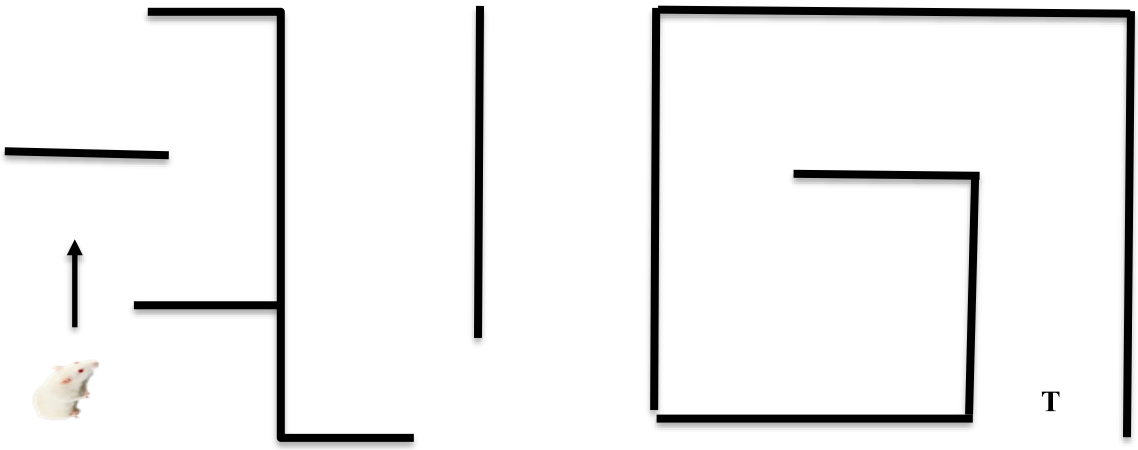


Figure 2 Schematic structure of the labyrinth. ↑ - rat direction in the maze; T - target.

The results showed that rats were able to find a path in the maze, increased under hypothyroidism, and when polyphenols were given, the time to find a path in the maze was reduced relative to hypothyroidism. For the development and maturation of the mammalian brain, the hormones of the thyroid gland are important both before and after birth. Serious anatomical and physiological abnormalities in brain functions are also observed in hypothyroidism and hyperthyroidism of the thyroid gland [25,26]. For many years, iodine deficiency has been considered a problem limited to certain geographic areas of the planet. The observation of alarming consequences of cognitive functions among the population of this region, having a low IQ level, has been determined by scientists. There have been cases of attention deficit hyperactivity disorder in children born to mothers with hypothyroidism. Thus, when a pregnant woman was found to have normal thyroid function, neurodefects in the fetus were considered unlikely [25]. Once the cognitive functions of rats were identified in the maze, healthy and hypothyroidism group rats were decapitated and the glucose content in their blood was determined using the *contour plus* glucometer, the erythrocyte and leukocyte content using the Goryayev chamber, and the erythrocyte agglutination rate using the phytogemoagglutination method. According to the results, it was found that the amount of glucose in the blood of rats of the control group is 5.69 ± 0.39 mmol/L, group of hypothyroid rats is 6.78 ± 0.4 mmol/L and hypothyroidism group increased by 20% compared to the blood of healthy rats. After that, when treat with polyphenols, the getasan polyphenols sum to 34% ($p \geq 0.01$), providin to 29% ($p \geq 0.01$), rutan ($p \geq 0.01$), *a.pyrifolia* ($p \geq 0.01$) and euphorbine polyphenols groups as well as by 24% ($p \leq 0.05$), *a.semennovii* polyphenols by 10% ($p \leq 0.05$), anacardine 1 polyphenols by 17% ($p \leq 0.01$), anacardine 2 polyphenols by 22% ($p \leq 0.01$), *r.glabra* plant polyphenols was found to have reduced the by 15% (5.88 ± 0.25 mmol/L). Decreased thyroid function has been found to have detrimental effects on cognitive functions regardless of age. This may be due to the decreased energy supply of the brain in hypothyroidism, i.e., decreased glucose consumption. As a result, there is a decrease in neurotransmission, processes necessary for memory and other higher brain functions. Low glucose absorption in the brain is usually accompanied by a decrease in mental and movement activity [27]. Decreased glucose absorption may also be associated with impaired function of members of the digestive system under hypothyroidism. According to research conducted in Nigeria, the weight gain observed in the hypothyroid small intestine and a significant increase in intestinal wall thickness may be associated with myxoedematous infiltration or fluid retention in the intestinal wall. In addition, infiltration of the hypothyroid intestine and thickening of the wall can slow down the rate of glucose transport, which leads to impaired glucose absorption [28]. In our hypothesis, brain cells need to receive the required amount of glucose for neurotransmission and memory. In hypothyroidism, glucose absorption decreases, and biologically active compounds cause glucose to be regenerated to some extent and normalize brain cognitive function. After that, the number of erythrocytes in the blood was determined.

Table 1 Effects of polyphenols on cognitive function (time to find a way through the maze) and some hematological parameters in healthy, hypothyroidism (mercazolil 1.2 mg/100 g), and groups of received polyphenols (10 mg/kg).

Experimental groups		Parameters n = 6; M ± m				
№		**Time to find your way through the maze (min).**	**Glucose (mmol/L)**	**Erytrocytes ($\times 10^6/\mu L$)**	**Agglutination (number of free erythrocytes that are not agglutinated ($\times 10^6/\mu L$)**	**Leucocytes ($\times 10^3/\mu L$)**
1	Control (healthy)	3.355 ± 0.44^{a}	5.69 ± 0.39^{a}	7.98 ± 0.26^{a}	2.65 ± 0.26^{a}	7.87 ± 0.49^{a}
2	Hypothyroidism	$5.33 \pm 0.43^{b**}$	$6.78 \pm 0.4^{b*}$	$6.17 \pm 0.27^{b***}$	$1.52 \pm 0.15^{b***}$	$4.76 \pm 0.298^{b***}$
3	Getasan (*Geranium sanguineum)*	$3.19 \pm 0.44^{ac**}$	$4.52 \pm 0.36^{cd***}$	6.48 ± 0.2^{cb}	1.7 ± 0.06^{cb}	$3.025 \pm 0.24^{cd***}$
4	Providin (*Vitis vinifera)*	$3.76 \pm 0.43^{ac*}$	$4.81 \pm 0.28^{ac***}$	6.02 ± 0.31^{cb}	1.26 ± 0.07^{cb}	$2.62 \pm 0.94^{cd***}$
5	Rutan (*Rhus coriaria)*	$3.285 \pm 0.35^{ac**}$	$5.22 \pm 0.23^{ac**}$	6.25 ± 1.02^{ab}	$0.93 \pm 0.03^{cd***}$	$3.625 \pm 0.44^{cd*}$
6	*Atraphaxis pyrifolia*	$3.47 \pm 0.3^{ac**}$	$5.17 \pm 0.23^{ac**}$	6.88 ± 0.65^{ab}	1.31 ± 0.08^{cb}	$3.1 \pm 0.387^{cd**}$
7	*Acer semennovii*	$3.4 \pm 0.3^{ac*}$	6.13 ± 0.27^{ab}	5.42 ± 0.71^{cb}	1.29 ± 0.1^{cb}	$2.625 \pm 0.71^{cd***}$
8	Euforbin (*Euforbio ferganensis)*	$3.7 \pm 0.4^{ac*}$	$5.06 \pm 0.46^{ac*}$	5.68 ± 0.31^{cb}	$0.93 \pm 0.02^{cd***}$	$2.592 \pm 0.27^{cd***}$
9	Anakardin 1 *(Pistacea vera)*	4 ± 0.5^{ab}	$5.67 \pm 0.29^{ac*}$	$5.25 \pm 0.39^{cb*}$	$1.1 \pm 0.07^{cd*}$	$2.683 \pm 0.44^{cd***}$
10	Anakardin 2 *(Pistacea vera)*	$3.98 \pm 0.47^{ac*}$	$5.32 \pm 0.17^{ac*}$	6.42 ± 0.11^{cb}	$1 \pm 0.04^{cd**}$	6.016 ± 0.684^{cd}
11	*Rhus glabra*	$3.56 \pm 0.23^{ac**}$	5.88 ± 0.25^{ab}	$6.98 \pm 0.4^{cb*}$	1.75 ± 0.14^{cb}	$3.625 \pm 0.358^{cd*}$

* - $p \leq 0.05$; ** - $p \leq 0.01$; *** - $p \leq 0.001$ n = 6; M ± m;

Different letters (a, b, c, d) indicate statistically significant differences among the groups ($p \leq 0.05$).

^{ab} - No statistically significant difference between the control group and the hypothyroidism group.

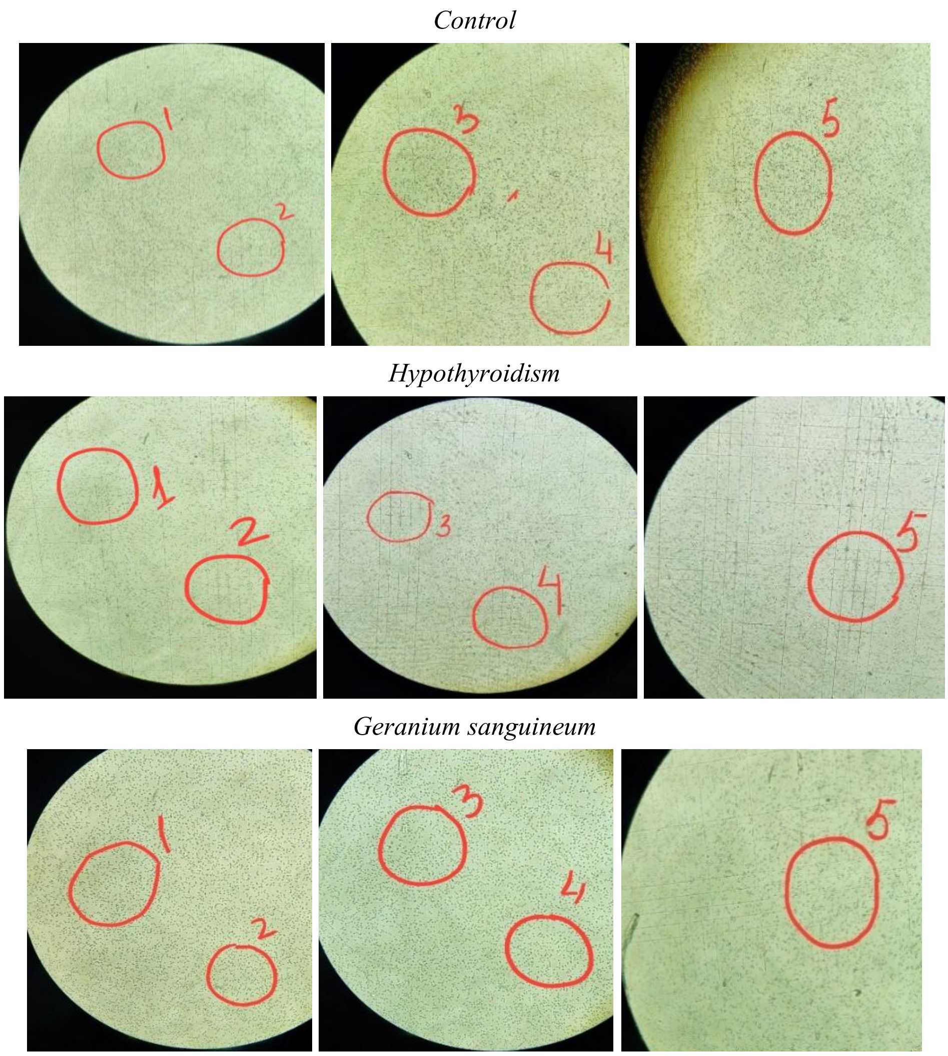
^{ac} - No statistically significant difference from the control group; significant difference from the hypothyroidism group.

^{cb} - Statistically significant difference from the healthy (control) group; no significant difference from the hypothyroidism group.

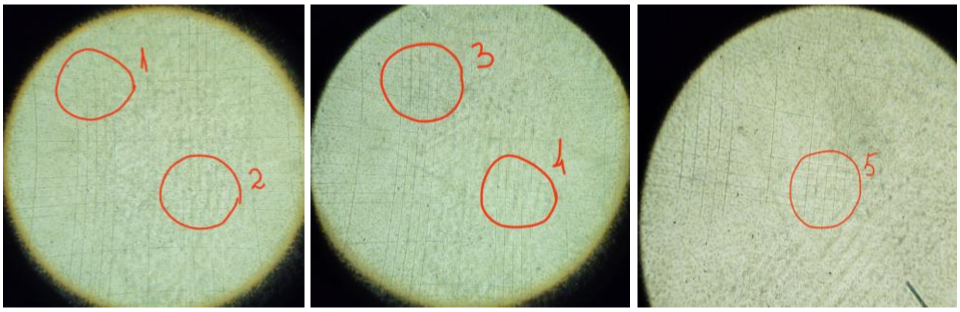
^{cd} - Statistically significant difference from both the control and hypothyroidism groups.

Changes in the rate of agglutination of erythrocytes, leukocytes and erythrocytes.

According to the results, the number of erythrocytes was found to be 22.7% lower than that of erythrocytes of rat blood in a healthy group (7.98 ± 0.26 compared to 6.17 ± 0.27). The difference between the groups is statistically significant ($p \leq 0.001$). When polyphenols of plants are given for 7 days to study the corrective effect on the state of erythrocyte depletion caused by hypothyroidism, it was found to increase the number of erythrocytes in the blood by 4.9% (6.48 ± 0.2) compared to the hypothyroidism group, when sent to the stomach the sum of *g.sanguineum* plant polyphenols. Providin polyphenols was found to have no corrective effect on the number of erythrocytes compared to the hypothyroidism group, instead lowering the number of erythrocytes by 2.4% (6.02 ± 0.31). The sum of rutan polyphenols was found to increase the number of erythrocytes by 1.3% (6.25 ± 1.02) compared to the hypothyroidism group, and the sum of polyphenols from the *atraphaxis pyrifolia* plant by 11.5% (6.88 ± 0.65) compared to the hypothyroidism group. When rat groups were tested for *acer semennoi,* euforbio, and ANK 1 polyphenols, the number of erythrocytes did not increase, but instead was found to have decreased by 12% (5.42 ± 0.71), 8% (5.68 ± 0.31), as well as 15% (5.25 ± 0.39), respectively, compared to the hypothyroidism group. It was found that the group of erythrocytes given the sum of ANK 2 polyphenols increased by 4% (6.42 ± 0.11), while the group given the polyphenols of the *r.glabra* plant increased by 13.1% (6.98 ± 0.4) ($p \leq 0.05$) (**Table 1**, **Figure 3**).



Atraphaxis pyrifolia



Rhus glabra

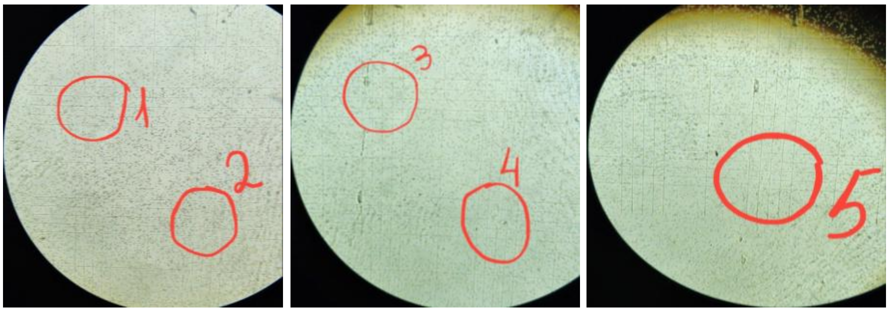


Figure 3 Count the number of erythrocytes in the microscope (healthy, hypothyroidism, as well as the best affected polyphenols were described).

Thyroid hormones play an important role in the process of cell development, their differentiation, and maintaining metabolic homeostasis. It is also important in the regulation of various hematological parameters. Including a significant effect on erythropoiesis [29]. The active form of thyroid hormones binds to specific members of the T_3 nuclear receptor family (TRa and TRb) and increases erythropoiesis by regulating the expression of the erythropoietin (EPO) gene, leading to the development of erythropoietin secretion by the kidneys. L-triiodothyronine increases the level of erythrocytes to promote the growth of erythroid colonies and deliver oxygen to tissues. Thus, dysfunction of thyroid hormones leads to various abnormalities of red blood cells (RBC) [30] and can cause anemia [29]. Some phytochemicals or herbs act directly to relieve anemia, while some, through their antioxidant activity, increase the property of oxidative stress resistance [31]. Polyphenols can affect anemia by regulating iron absorption and metabolism in several ways. First, the consumption of foods or drinks rich in certain polyphenols limits the absorption of iron. This process may result from the risk of iron deficiency caused by polyphenol consumption due to the iron chelating properties of polyphenols [32]. Secondly, some polyphenolic compounds have a regulatory effect on iron by modulating gepcidin, a hormone produced by the liver that regulates iron production. Gepsidine is a systemic iron regulator that controls the absorption of iron from the intestine and the mobilization of iron from the reticuloendothelial system [33]. In the studies we have carried out, the decrease in the number of erythrocytes caused by hypothyroidism may have been the result of a decrease in the effect of thyroid hormones on the formation and maturation of blood cells. Polyphenols, which increased the number of erythrocytes compared to the hypothyroidism group, stimulated the absorption of iron from the intestine, while polyphenols, which lowered the number of erythrocytes compared to the hypothyroidism group, may possibly have iron-absorbing properties.

In contrast, leukocyte counts were found to have decreased from 7.87 ± 0.49 to 4.76 ± 0.298 and it was 39.5% reduction in the hypothyroidism group when compared to healthy rats ($p \leq 0.001$). These results correspond to data obtained by other authors who used slightly different methods of hypothyroidism induction.

When correcting with polyphenols for 7 days, a further decrease in the number of leukocytes was observed in all groups except anacardin 2 polyphenols. The group of given the polyphenols of the *g.sanguineum* plant is 32% ($p \leq 0.001$), the polyphenols of providin are

45% ($p \leq 0.001$), and the polyphenols of rutan are 24% ($p \leq 0.05$), *a.pyrifolia* plant polyphenols by 35% ($p \leq 0.01$), *a.semennovii* polyphenols by 45% ($p \leq 0.001$), *euphorbine* polyphenols by 46% ($p \leq 0.001$), anacardine by one 44%, in the group given polyphenols of *r.glabra* plants, the number of leukocytes in the blood decreased by 24%. Among the selected polyphenols, it was found that only anacardic 2 increased the number of leukocytes in the blood by 26.4% compared to hypothyroidism (**Table 1**). Among polyphenols used experimentally, polyphenols other than ANK 2 did not have a corrective effect on leukocytes when administered for 7 days, unlike other indications. Considering that it has a positive effect on other indicators, these polyphenols may have a corrective effect on leukocytes, either when administered in a continuous period or other doses, or when used together with drugs that act precisely on leukocytes. The research we have done sets the stage for new research to study the effects of polyphenols on leukocytes. Data on the dependence of leukocyte development on thyroid hormones has been proven in several studies. In mice with thyroid dysfunction observed, the number of B-lymphocytes is restored when the treat with thyroid hormones [34] and a decrease in the number of T and B lymphocytes, macrophages and granulocytes in the spleen and other lymphoid organs is observed in experiments that show that the latter leads to the destruction of genes responsible for thyroid hormone receptors [35]. In addition, in animals where there is a decrease in the activity of thyroid hormones, the activity of bone marrow cells decreases, another of the reasons for the decrease in the number of leukocytes. there may also be a possibility of a violation of the function of general lymphoid progenitor cells [34,36].

During the experiment, the rate of agglutination of erythrocytes in the blood was studied using the phytogemagglutination method. The results found that the number of non-agglutinated free erythrocytes decreased by 43% compared to the number of erythrocytes of rats in a healthy group (from 2.65 ± 0.26 to 1.52 ± 0.15) ($p \geq 0.01$) in a group of rats with hypothyroidism. After that, polyphenols were given to rats with induced hypothyroidism. In a group given polyphenols of the *g.sanguineum* plant, the amount of free erythrocytes that are not agglutinated compared to the hypothyroidism group is 12% (from 1.52 ± 0.15 to 1.7 ± 0.06), the polyphenols of the *r.glabra* plant, on the other hand, were found to have increased by 14% (from 1.52 ± 0.15 to 1.75 ± 0.14) ($p \geq 0.05$). However, all other polyphenols did not have a corrective effect on the agglutination rate of the erythrocyte in hypothyroid rats (**Table 1**). According to the WHO, the prevalence of anemia is 24.8% worldwide and is more frequent in developing countries. The prevalence of anemia in subclinical hypothyroidism was 26.6% and 73.2% in overt hypothyroid people. Thus, the frequency of anemia in the population with hypothyroidism is much higher than in the general population. Therefore, the presence of hypothyroidism is one of the risk factors for anemia [37].

Changes in weight parameters in the groups with hypothyroidism and receiving polyphenols

It has long been known that thyroid hormones (TH) regulate energy metabolism [38]. There is an important interaction between thyroid function, weight control, and obesity [39]. During our studies, when the weight of rats in the healthy and hypothyroid groups was compared, it was found that the mass of rats in the hypothyroid group increased from 200 ± 8.85 to 242 ± 9.3. A significant 20% increase was observed in comparison to rats in the healthy group ($p \geq 0.01$). During the experiment, it was found that the results of the correction of this condition with polyphenols showed a 15% decrease in mass compared to the hypothyroidism group in rat groups where getasan, providin, and rutan polyphenols were given ($p \geq 0.05$). In groups given *a.pyrifolia*, euphorbine, and ANK 1 ($p \geq 0.05$) polyphenols, the rats had a total weight of 13%, the *acer semennovii* polyphenols 4%, anacardine two 10% ($p \geq 0.05$), *r.glabra* was found to have reduced total weight by 14% ($p \geq 0.01$) (**Figure 4**). Patients with thyroid dysfunction often experience symptoms of metabolic dysregulation, including fatigue and weight change [15]. Weight gain and reduction associated with thyroid dysfunction may be associated with hypothyroidism and hyperthyroidism, respectively [40,41]. Hypothyroidism is characterized by decreased food intake and weight gain despite loss of appetite [42]. Weight gain during the study of groups of patients with thyroid diseases may be due to the balance of thyroid diseases [39]. Due to the low metabolic rate, it is generally assumed that long-term patients with overt hypothyroidism are overweight and gain body weight during severe hypothyroidism. The main mechanism of such an increase in body weight may be due to the accumulation of water between the tissues, and not fat, as expected [43].

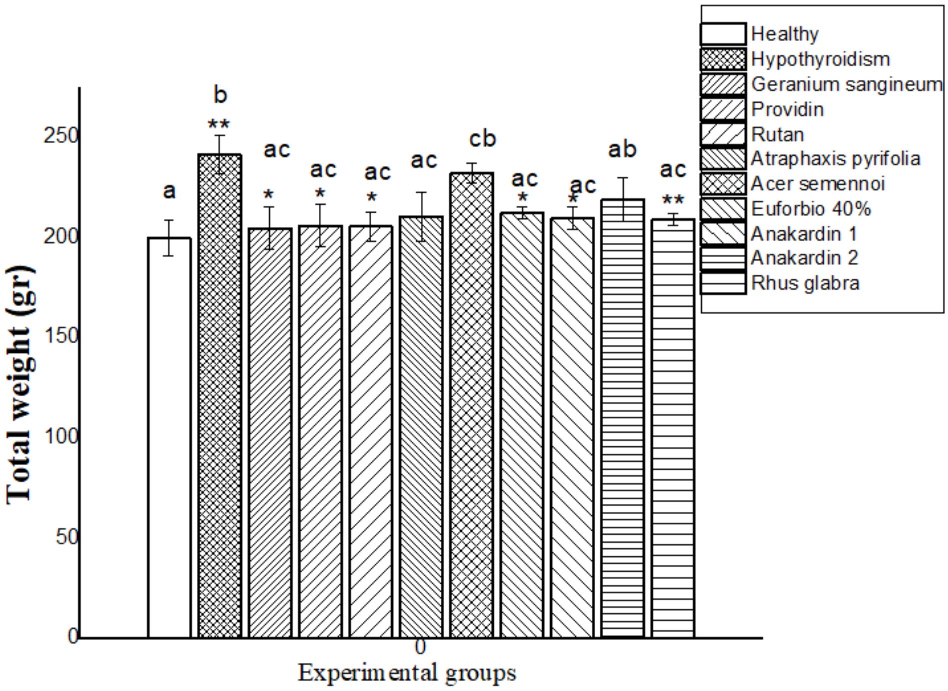


Figure 4 Changes in body weight (gr) in healthy, hypothyroidism (mercazolyl 1.2 mg/100 g) and polyphenol (10 mg/kg) intake groups. * - $p \leq 0.05$; ** - $p \leq 0.01$; n = 6; M ± m Different letters (a, b, c, d) indicate statistically significant differences among the groups ($p \leq 0.05$).
ab - No statistically significant difference between the control group and the hypothyroidism group.
ac - No statistically significant difference from the control group; significant difference from the hypothyroidism group.
cb - Statistically significant difference from the healthy (control) group; no significant difference from the hypothyroidism group.

After that, changes in the weight of the thyroid gland were studied in hypothyroidism as well as when corrected with polyphenols. According to the results, hypothyroidism group showed a 33.8% increase (from 0.83 ± 0.048 to 1.1 ± 0.06) compared to controls ($p \leq 0.01$). When polyphenols of *g.sanguineum* (0.9 ± 0.08), *a.pyrifolia* (0.91 ± 0.06), *r.glabra* (0.9 ± 0.075) plants are given, thyroid gland weight was observed to decrease by 18% compared to the hypothyroidism group ($p \geq 0.05$). While in groups given providin and euphorbin polyphenols, a 27% decrease in thyroid mass compared to the hypothyroidism group was observed (0.81 ± 0.07) ($p \geq 0.05$). In contrast, given the polyphenols rutan ($p \leq 0.001$) and anacardine 1, it was found to be 35% reduced compared to the hypothyroidism group (0.73 ± 0.04) ($p \leq 0.01$).

Acer semennovii as well as anacardine 2 polyphenols, were observed to decrease by 19% (0.9 ± 0.06) and 23% (0.85 ± 0.07), respectively, in the given groups ($p \geq 0.05$) (**Figure 5**).

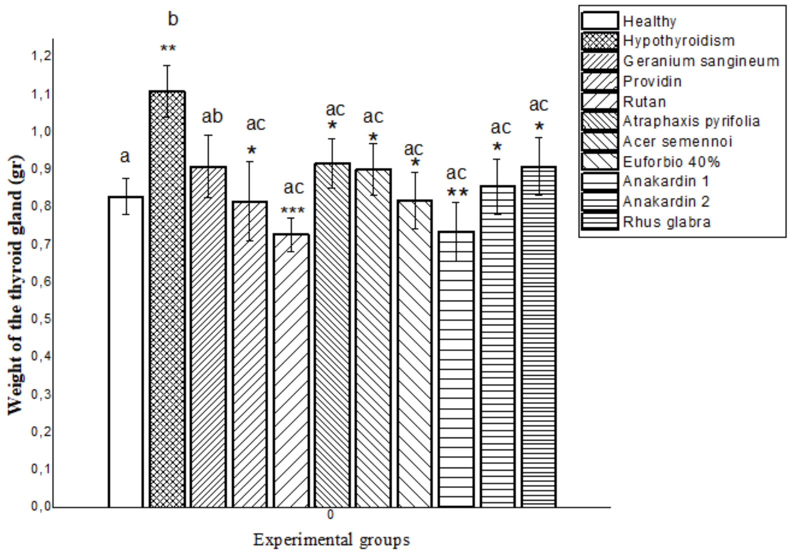


Figure 5 Comparison of thyroid gland mass in groups healthy, hypothyroidism (mercazolil 1.2 mg/100 g) as well as receiving polyphenols (10 mg/kg) * - $p \leq 0.05$; ** - $p \leq 0.01$; *** - $p \leq 0.001$ n = 6; M ± m.
Different letters (a, b, c, d) indicate statistically significant differences among the groups ($p \leq 0.05$).
ab - No statistically significant difference between the control group and the hypothyroidism group.
ac - No statistically significant difference from the control group; significant difference from the hypothyroidism group.

The weight of the body or organ is an integral indicator of its condition. Thus, the increase in thyroid weight observed in hypothyroidism is not only a sign of its specific pathologies, but also a sign of deterioration in the condition of the whole organism [43]. Thyroid hormones affect almost all organs in the body and regulate basal metabolism. The intestines and internal organs are no exception. Disorders of thyroid function can cause many gastrointestinal pathologies. Hyperthyroid patients may experience decreased stomach size and increased stomach weight in the hypothyroid, increased gastric emptying rate, and muscle swelling [28]. In addition, patients with hypothyroidism of the thyroid gland may experience dyslipidemia, mood swings, cognitive deficits, cardiac dysfunction, osteoporosis, and most importantly, weight gain [44]. Other findings include impaired thyroid hormone function, skin changes, in particular functional changes in the dermis, increased dryness, and exfoliation. This disrupts the quality of life which leads to stress and depression [45].

Although it has been proven that there is a complex interaction between the thyroid and the immune system, later in the study, weight changes in the thymus and spleen, which modulate the immune system organs, were also studied in thyroid hypothyroidism. According to the results, the weight of the thymus in healthy (0.26 ± 0.02) and hypothyroid groups (0.039 ± 0.01) was observed to increase by 50.6% ($p \leq 0.001$), (**Figure 6**), compared to the healthy group in the hypothyroidism group, and the mass of the spleen, by 6% (from 0.96 ± 0.06 to 1.02 ± 0.08) (**Figure 7**). When polyphenols are given, however, the thymus mass is relative to the hypothyroidism group of *g.sanguineum* polyphenols by 37%, ($p \geq 0.001$), polyphenols of the plant *a.pyrifolia*, *r.glabra* were found to be 30%, reduced ($p \leq 0.001$). In a group given the sum of rutan polyphenols, a change in the mass of the thymus was hardly observed. It was found that the mass of the thymus decreased by 8% in the group given euphorbine and by 48% ($p \geq 0.001$) in the group given anacardine 2. When the mass of the spleen is determined in groups of rats given these polyphenols, *g.sanguineum* as well as ancardine 2 polyphenols have a spleen weight of 15% compared to the hypothyroidism group, rutan polyphenols of 13%, *a.pyrifolia* as well as polyphenols of the euphorbine plant are found in groups at 9% and 10%, respectively, in a group of polyphenols of the r.glabra plant given, however, a decrease of 3% was observed (**Figure 7**).

The polyphenols *providin*, *Acer semennovii,* and *anacardin 1* did not have a corrective effect on thymus and spleen weight compared to the hypothyroidism group, but were instead found to significantly gain their mass (**Figures 6** and **7**).

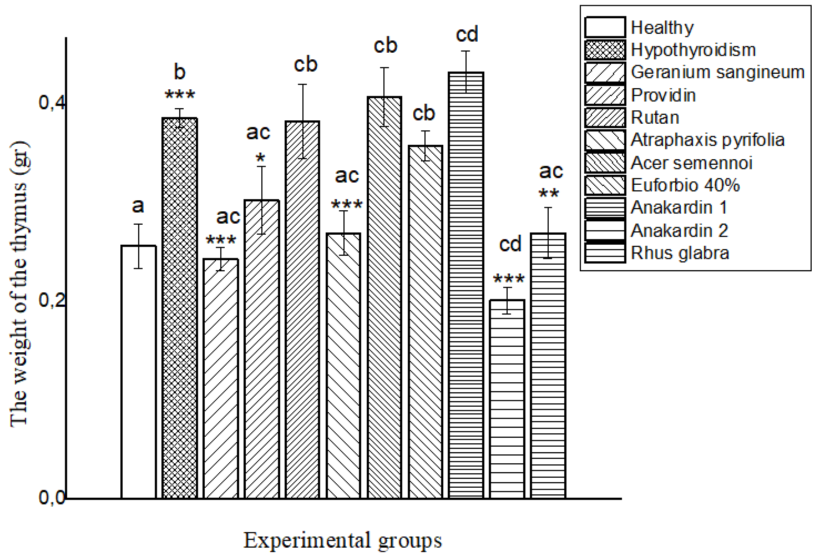


Figure 6 Comparison of thymus mass in healthy, hypothyroidism (mercazolil 1.2 mg/100 g), as well as polyphenols (10 mg/kg) taking groups * - $p \le 0.05$; ** - $p \le 0.01$; *** - $p \le 0.001$ n = 6; M ± m Different letters (a, b, c, d) indicate statistically significant differences among the groups ($p \le 0.05$).
ac - No statistically significant difference from the control group; significant difference from the hypothyroidism group.
cb - Statistically significant difference from the healthy (control) group; no significant difference from the hypothyroidism group.
cd - Statistically significant difference from both the control and hypothyroidism groups.

There is extensive literature showing important interactions between thyroid hormones and the immune system that depend on mammalian development and function. Similarly, in most vertebrates, thyroid hormones are involved in the development and maturation of the immune system. Thyroid receptors have been identified on the surface of the plasma membrane of lymphocytes, and the fact that lymphocyte activity can be controlled by thyroid hormones in rats is clear proof of this. Thyroid hormones have been found to affect B-lymphopoiesis, thymus development and physiology, and mammalian cellular and humoral immunity [46]. These findings suggest 2 distinct pathogeneses for thymus enlargement in patients with thyroid disease. While thymus tissue dilation seems to depend on the hyperthyroid state, lymphoid hyperplasia is more associated with Graves' disease-based immune abnormalities. Thymulin is a thymic protein that plays a role in lymphocyte differentiation and has been described as having increased function in patients with hyperthyroidism and decreased function in patients with hypothyroidism, and may play a role in the development of lymphoid hyperplasia. Experimental studies have observed that patients with hyperthyroidism may experience peripheral lymphocytosis, diffuse lymphadenopathy, and splenomegaly, i.e., enlarged spleen [47].

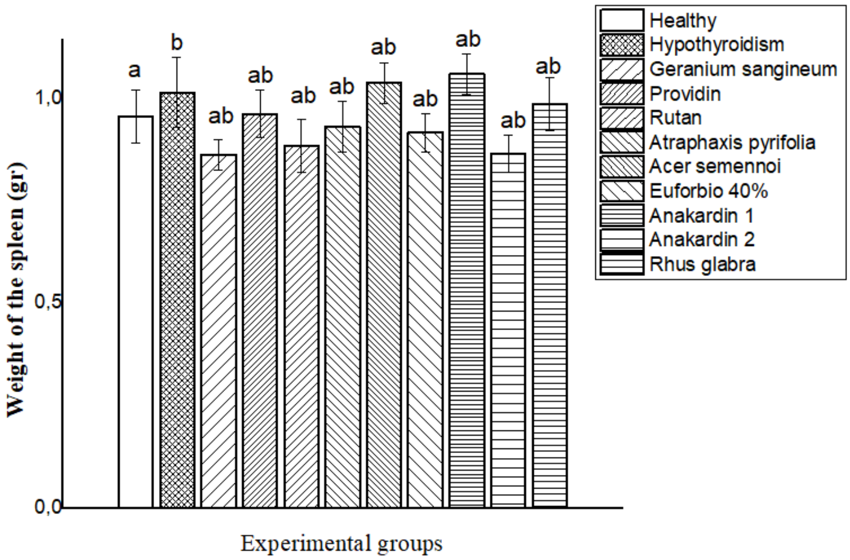


Figure 7 Comparison of spleen mass in groups healthy, hypothyroidism (mercazolil 1.2 mg/100 g) as well as receiving polyphenols (10 mg/kg), n = 6; M ± m. Different letters (a, b, c, d) indicate statistically significant differences among the groups ($p \leq 0.05$).
ab - No statistically significant difference between the control group and the hypothyroidism group.

The spleen is a secondary lymphoid organ that functions to filter blood and it contains a quarter of all lymphocytes in the body. According to the structure of the spleen, the periarteriolar lymph consists of a red pulp consisting of T-lymphocytes formed in the shell and B-lymphocytes formed from primary and secondary follicles, macrophages and venous sinuses, and a unique interrelated structure - the marginal zone [48]. In experiments on hypothyroid puppies in Serbia, when there is a change in the tissue of the spleen, it is observed that the volume density of primary lymph follicles decreases, and the number of T and B lymphocytes decreases significantly [34]. Even the decrease in the number of leukocytes in the blood in the experiment we conducted can also be, perhaps, for this reason. Another important aspect of experiments on puppies of the hypothyroidism model is that in hypothyroidism, the density of the volume of the red pulp of the spleen increases. The red pulp is composed of reticular cells, endothelial cells, and macrophages, and acts mainly as phagocytic cells responsible for removing old and damaged erythrocytes [49]. It can be assumed that the volume density of red pulp is most likely due to an increase in the number of macrophages, but an increase in blood vessels or their density can also contribute to this change. When spleen changes associated with thyroid hormone deficiency are studied, the main reason for the occurrence of hypothyroidism-related myxedema may be the accumulation of hyaluronic acid, a glycosaminoglycan. In our experiment, it was not clear whether myxedema occurred. But some findings suggest that hyaluronic acid accumulates in the internal organs during hypothyroidism development [50]. The increase in the mass of the spleen during the experiments we conducted can be explained by these phenomena [34].

In the case of hypothyroidism of the thyroid gland, as well as during the study of its correction with several polyphenols, the weight of the adrenal glands was examined. According to him, the hypothyroidism group showed an increase in the weight of the right adrenal gland by 21% compared to the healthy group (from 0.03 ± 0.002 to 0.038 ± 0.004), and the weight of the left adrenal gland by 23% (from 0.032 ± 0.004 to 0.04 ± 0.003). In the case of proofreading with polyphenols, however, *g.sanguineum* polyphenols have a 18% corrective effect on the mass of the right adrenal gland compared to the hypothyroidism group (to 0.032 ± 0.004), and 15% on the weight of the left adrenal gland (to 0.034 ± 0.002). *V.vinifera* polyphenols have been found to have a 5% corrective effect on the right adrenal gland (to 0.037 ± 0.002) and a 13% corrective effect on the left adrenal gland (0.03 ± 0.001). *R.coriaria* polyphenols had a 10% corrective effect on the right renal gland (0.035 ± 0.005) and 20% on the left renal gland (to 0.032 ± 0.0033). *A.pyrifolia* polyphenols, on the other hand, were observed to have a 15% corrective effect on the right adrenal gland (to 0.033 ± 0.0033) and a 13% corrective effect on the left adrenal gland (0.035 ± 0.004). In the group of given *a.semennovii* polyphenols, there was almost no change in the mass of the right adrenal gland compared to the hypothyroidism group, while the weight of the left adrenal gland was observed to decrease by 17% (0.033 ± 0.002) compared to the hypothyroidism group. Euphorbine and anacardine 1 polyphenols have also been found to reduce right and left adrenal glands by 23% - 24% compared to hypothyroidism (to 0.029 ± 0.002) ($p > 0.05$). While the polyphenols of the *r.glabra* plant had no significant effect on the right adrenal gland compared to the hypothyroidism group, the left adrenal gland was found to have a 5% decrease compared to the hypothyroidism group (to 0.038 ± 0.003). Of all the polyphenols used, anacardine 2 polyphenols did not have a corrective effect on both adrenal glands, but were instead found to increase the weight of the right adrenal gland by 10% compared to the hypothyroidism group, and the mass of the left adrenal gland by 15% (to 0.044 ± 0.005) (**Figure 8**).

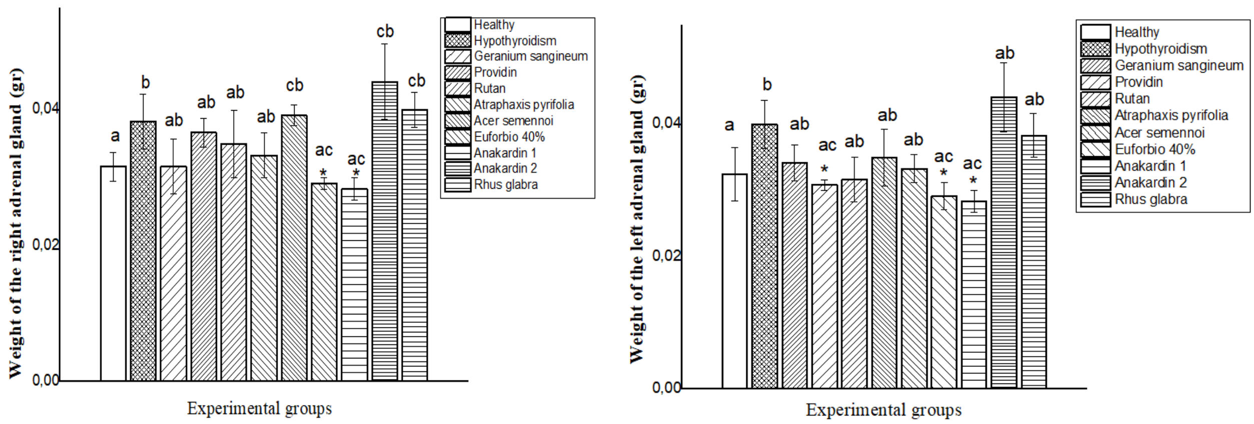


Figure 8 Comparison of adrenal gland mass in healthy, hypothyroidism (mercazolil 1.2 mg/100 g) as well as polyphenols (10 mg/kg) - taking groups * - $p \leq 0.05$; ** - $p \leq 0.01$; n = 6; M ± m Different letters (a, b, c, d) indicate statistically significant differences among the groups ($p \leq 0.05$).
ab - No statistically significant difference between the control group and the hypothyroidism group.
ac - No statistically significant difference from the control group; significant difference from the hypothyroidism group.
Cb - Statistically significant difference from the healthy (control) group; no significant difference from the hypothyroidism group.

There is theoretical speculation that there may be a certain connection between the thyroid gland and the adrenal glands. This is because the amino acid tyrosine is a common substrate for the formation of thyroid and steroid hormones. The weight of the thyroid gland and adrenal glands can also be associated mainly with iodine consumption, its chemical nature, and dosage. In hypothyroidism of the thyroid gland, an increase in the weight of the thyroid gland as well as the adrenal gland allows us to assume that there is a functional relationship between these organs [43]. In the case of an increase in organ weight, some polyphenols were found to have a corrective effect, while some were found to have the opposite from the mass of the hypothyroid group as well. Weight loss after overt hypothyroidism therapy is associated with the release of bound water (myxoedema) in tissues. The mechanism of this excess weight gain is not fully explained, and new studies on the relationship between L-triiodtironine therapy and weight will be discussed. The interaction between weight control and thyroid disease treatment is important for many patients and should be studied in more detail [39].

Conclusions

The thyroid gland is an endocrine gland that regulates all metabolic processes in the body. Thyroid dysfunction, on the other hand, can also cause various side effects in the body. During our studies, there was a decrease in cognitive functions in experimental animals in hypothyroidism of the thyroid gland (due to the nature of being able to find a way in the labyrinth), as well as an increase in glucose in the blood. During the experiment, changes in cognitive functions under the conditions of experimental hypothyroidism were shown among polyphenols *g.sanguineum* had the best corrective effect.

Thyroid hormones are also important for the formation, maturation and normal function of blood cells. In contrast, according to work with polyphenols, compared to the number of erythrocytes, only, *g.sanguineum, r.coriaria, a.pyrifolia, ANK 2 and r.glabra* plants contain polyphenols, while agglutination events include, of polyphenols from *g.sanguineum* and *r.glabra* plants have been found to increase the number of erythrocytes in part compared to the hypothyroidism group by having a corrective effect. In contrast, the number of leukocytes has been found to only correlate with the ank 2 polyphenol hypothyroidism group.

The overall body weight was found to be positive in the groups in which all polyphenols were taken, as determined by the process of correction with polyphenols. Thyroid mass was also observed to be lowered by all polyphenolic compounds, but it was found that the thyroid mass was also lowered from the norm in groups that received the sum of *rutan* and *ANK 2* polyphenols. As for members of the immune system, *providin, acer semennovii* and *ANK 1* plant polyphenols did not have a corrective effect on the mass of the spleen and thymus, on the contrary, there was a significant increase in the weight of organs to the hypothyroidism group. The groups given the remaining polyphenols were found to each have a corrective effect at certain percentages. *ANK 2* as well as to the mass of the adrenal glands polyphenols of *r.glabra* plant's polyphenols were negatively affected. The remaining polyphenols were found to have a corrective effect on the hypothyroidism group. The results of the studies we conducted closely coincide with the results of the work of other authors who used slightly different methods of induction of hypothyroidism performed on a global scale.

Acknowledgements

We thank to the employees of the laboratory of protein and peptide chemistry of the Institute of Bioorganic Chemistry named after A. Sadykov the Academy of Sciences of the Republic of Uzbekistan for the separation of polyphenols used in the implementation of this research.

Ethics approval

All experimental procedures were approved by the rules of the "European convention for the protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 1986) and the Institutional ethical committee in compliance of the Republic Uzbekistan legislation.

Declaration of Generative AI in Scientific Writing

During the preparation of this scientific manuscript, the artificial intelligence used solely for text editing purposes. All other tasks-including the development of scientific ideas, data collection and analysis, drawing conclusions, and finalizing the manuscript-were entirely carried out independently by the authors. Authors personally reviewed and approved AI -assisted edits and take full responsibility for the accuracy and content of the scientific article.

CRediT Author Statement

Sh.R. Mamadaliyeva conducting experiments, data analysis, writing an article, **N.G.Abdulladjonova** getasan, providin, euforbin extraction of polyphenols and determination of their chemical structure, in addition checking of the data, **K.V. Raimova** separation of polyphenols of the plant acer semennovii, atraphaxis pyrifolia and determination of their chemical structure, **R.N. Rakhimov** separation of polyphenols of Rhus coriaria and Rhus glabra plants, determination of their chemical structure, **R.R.Makhmudov** separation of polyphenols Anacardin 1, Anacardin 2 and determination of their chemical structure, **U.R. Yusupova** planning, monitoring experiments, checking the data of the article.

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