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INVESTIGATION OF THE EFFECT OF *XANTHIUM STRUMARIUM L.* EXTRACT ON THE LEVEL OF THYROID-STIMULATING HORMONES AND MASS COEFFICIENT OF RAT THYROID GLAND

Abstract. Iodine deficiency disorders (IDD) are pathological states caused by the reduction of iodine intake. These diseases include iodine-deficient hypothyroidism, diffuse nontoxic goiter, nodular goiter, functional autonomy of thyroid. Goiter is one of the most common thyroid disorders. Iodine deficiency is the most common cause of these diseases. It is evident that the most adverse effects arise with early stage of human development that moves through the stages of embryofoetal development infancy, childhood, adolescence, and adulthood. The main etiologic factor of this pathology is a lack of iodine in biosphere; it is almost unchanged. Therefore the prevention and control of iodine deficiency disorders among the population in iodine deficient regions is nagging health and social problem.

It is known that seafood (seaweed, shellfish, mollusks, and fish) is the primary natural source of iodine. Other food products contain insignificant amount of this micro-element. Brown algae that is rich in iodine stimulates the thyroid gland and regulates its metabolism. In addition to seaweeds and seafood there are plants that are source of iodine and used for pharmacological correction and prevention of IDD. These plants contain substances that have an effect not on the thyrocytes but on the cells of immune system present in gland and responsible for the processes of tissue regulation. *Xanthium strumarium L.* is relevant to plants that have a great impact on the pathogenesis of the respective diseases. That's why this plant was chosen as a study object.

Extract of *Xanthium strumarium L.* has been obtained. The amount of total iodine (0.21%) has been performed by titrimetric method with sodium thiosulfate (0.01M) according to the requirements of the monograph "Laminaria[N]" of the State Pharmacopoeia of Ukraine.

The influence of *Xanthium strumarium L.* extract on the level of thyroid-stimulating hormones in serum and mass coefficient has been investigated on the model of perchlorate-induced hypothyroidism. It has been established that *Xanthium strumarium L.* extract was inferior to efficacy compared to reference drug "Iodomarin® 100". Taking into consideration mechanism of action of sodium perchlorate, it can be assumed that inorganic iodine contained in the tablets of "Iodomarin® 100" had higher ability to penetrate into the tissues of thyroid gland compared to other mostly organic forms of iodine in *Xanthium strumarium L.* extract. This inorganic form of iodine results in lowering of local iodine deficiency and reduces signs of pathology.

Key words: iodine deficiency disorders, *Xanthium strumarium L.*, extract, thyroid-stimulating action.

Iodine deficiency disorders (IDD) are a major challenge to the health of populations all over the world. According to estimates of WHO and UNICEF more than billion of people were at risk of IDD, 300 millions were affected by goiter. That's why primary health care and control of IDD was included into the international programs together with such diseases as AIDS, infantile paralysis and tuberculosis [1, 2].

Prevention and control of iodine deficiency disorders among the population in iodine deficient regions are one of the biggest worldwide public health problems. IDD elimination is a top-priority task for many countries worldwide including Ukraine [3].

Iodine is essential for the production of thyroid hormones, for normal growth, and for brain development. Iodine is naturally present in seawater and in the soil, and the iodine content of the soil

determines its content in vegetables, milk, and eggs. Fish, seafood, and algae are good sources of iodine. Brown algae that is rich in iodine stimulates the thyroid gland and regulates its metabolism [4, 5].

In addition to seaweeds and seafood there are plants that are source of iodine and used for pharmacological correction and prevention of IDD. These plants contain substances that have an effect not on the thyrocytes but on the cells of immune system present in gland and responsible for the processes of tissular regulation. These plants are used individually or in combination. *Xanthium strumarium L.* belongs to the plants that effect the aetiopathogenesis. Therapeutic benefit of this plant is evident as at the toxic goiter and at the Riedel disease [6].

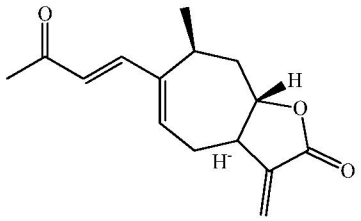
Xanthium strumarium L. (Family: *Compositae*) is a cocklebur or burweed commonly found as a weed in roadsides, rice fields, hedges throughout the tropical parts of India, South America, Europe, Caucasus, some regions of Asia and Russia. This plant is the most abundant and widely spread out in Australia, Africa, and Oceania and also in South America [7].

The plant is successfully used in treating thyroid disorders; it has evident antiseptic, antithermic, anti-inflammatory, fungicidal and diaphoretic properties. People's experience points to the fact that *Xanthium strumarium L.* is really therapeutically effective agent. But this plant is not used in Ukrainian academic medicine.

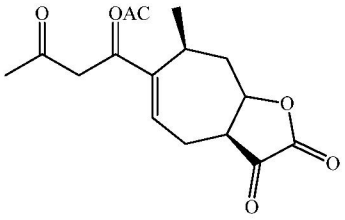
The aerial parts of the plant contain a mixture of unidentified alkaloids, which are said to be toxic. Besides alkaloids, the aerial parts of the plant contain sesquiterpene lactones, viz. xanthinin; its stereo-isomer, xanthumin, xanthatin (deacetylxanthinin); a toxic principle, a sulphated glycoside: xanthostru-marin, atractyloside, carboxyatractyloside; phytosterols, xanthanol, isoxanthanol, xanthinosin, 4-oxo-bedfordia acid, hydroquinone; xanthanolides; caffeoylquinic acids; α and γ-tocopherol; thiazinedione, 4-oxo-1(5),2,11,(13)-xanthatriene-12,8-olide, known as "deacetyl xanthumin" an antifungal compound; linoleic acid. The main toxic compound isolated from the plant has been identified as carboxyatracty-loside, a kaurene glycoside previously called xanthostrumarium. In addition to carboxyatractyloside CAT, potentially toxic ingredients include several sesquiterpene lactones (e.g. guaianolides, germacranolides, and elemanolides). Aerial parts contain three xanthanolide and xanthanetype sesquiterpenoids, 11α,13-dihydroxanthatin, 4β,5βepoxyxanthatin-1α,4α-endoperoxide, 1β,4β,4α,5α–diepoxy xanth-11(13)-en-12-oic acid, a dimeric xanthanolide, sesquiterpene lactones, 8-epixanthatin, 2-epixanthumin and 8-epi-xanthatin-5β-epoxide. The phenols isolated are caffeic acid, potassium3-O-caffeoylquinate, 1-O-caffeoyl quinic acid, chlorogenic acid, 4-O-caffeoylquinic acid, 1,4-di-O-caffeoylquinic acid, 1,5-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinicacid, 4,5-di-O-caffeoylquinic acid, 1,3,5-tri-O-caffeoylquinic acid, 3,4,5-tri-O-caffeoylquinic acid, and cynarin. The toxic principles of the seeds are hydroquinone, choline and a third more toxic unidentified compound. Besides these, the seeds also contain considerable amount of iodine. The fruits are rich in vitamin C [8, 9]. Thiazinediones isolated from the fruits are 7-hydroxy methyl-8,8-dimethyl4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-dglucopyranoside, 2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-Oβ-d-gluco-pyranoside, 7-hydroxymethyl-8,8-dimethyl-4,8- dihydrobenzo[1,4]thiazine-3,5-dione, 7-hydroxy-methyl-8,8- dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-(2-Ocaffeoyl)-β-d-glucopyranoside, ferulic acid, formononetin and ononin. The powdered shell of fruit can be used for making activated carbon. The shells contain 15.9% pentosans and can be used as a raw material for the synthesis of furfural. The young fruit contains glucose, fructose, sucrose, organic acids, phosphatides, potassium nitrate, β-sitosterol, γ-sitosterol, β-d-glucoside of β-sitosterol called strumaroside. The total free amino acid content is 1.65%. It includes amino-n-butyric acid, arginine, aspartic acid, cystine, glutamic acid, me-thionine, proline, tryptophan in micromoles per milligram dry weight [10, 11]. The structural formulas of the most important biologically active substances of *Xanthium strumarium L.* are given in the figure.

Additionally, *Xanthium strumarium L.* contains a significant quantity of iodine-containing compounds that regulate functional activity of thyroid gland [11, 12].

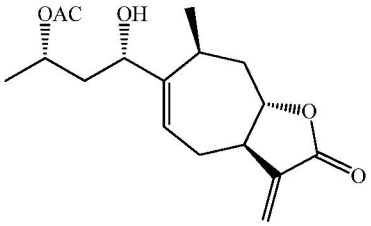
Materials and methods. Extract of *Xanthium strumarium L.* was obtained in accordance with general scheme. Air-dried herbal raw material, reduced in size of particles passing through the 3-4 mm sieve openings, was added to the extractor. Hot water extraction was performed at raw material to extracting solvent ratio of 1:10 till complete recovery of biologically active substances taking into account adsorption coefficient of extracting solvent.



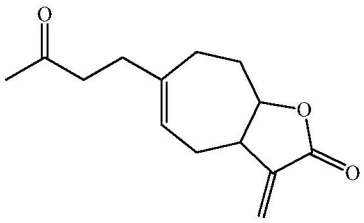
(-)-xanthatin



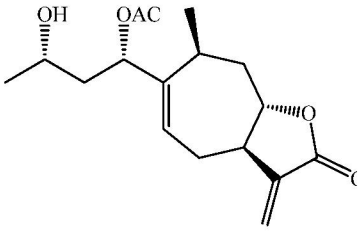
xanthinin



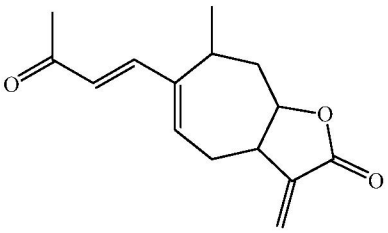
xanthanol



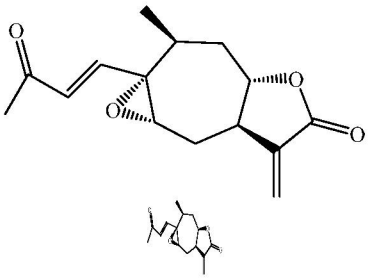
xanthinosin



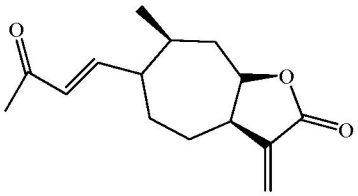
isoxanthanol



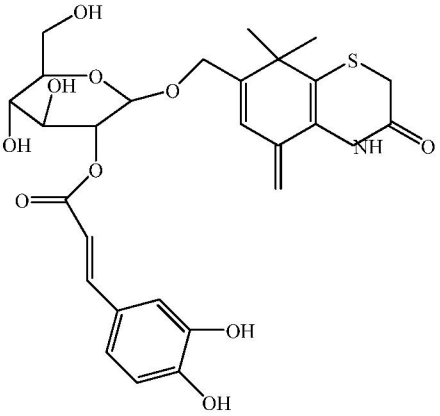
deacetyl xanthumin



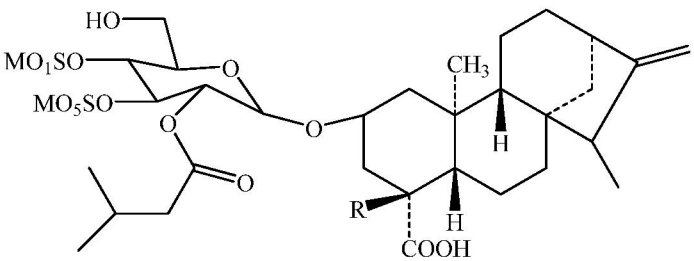
5- epixanthatin-5β-epoxide



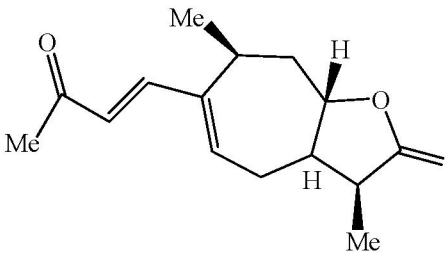
8-epixanthatin



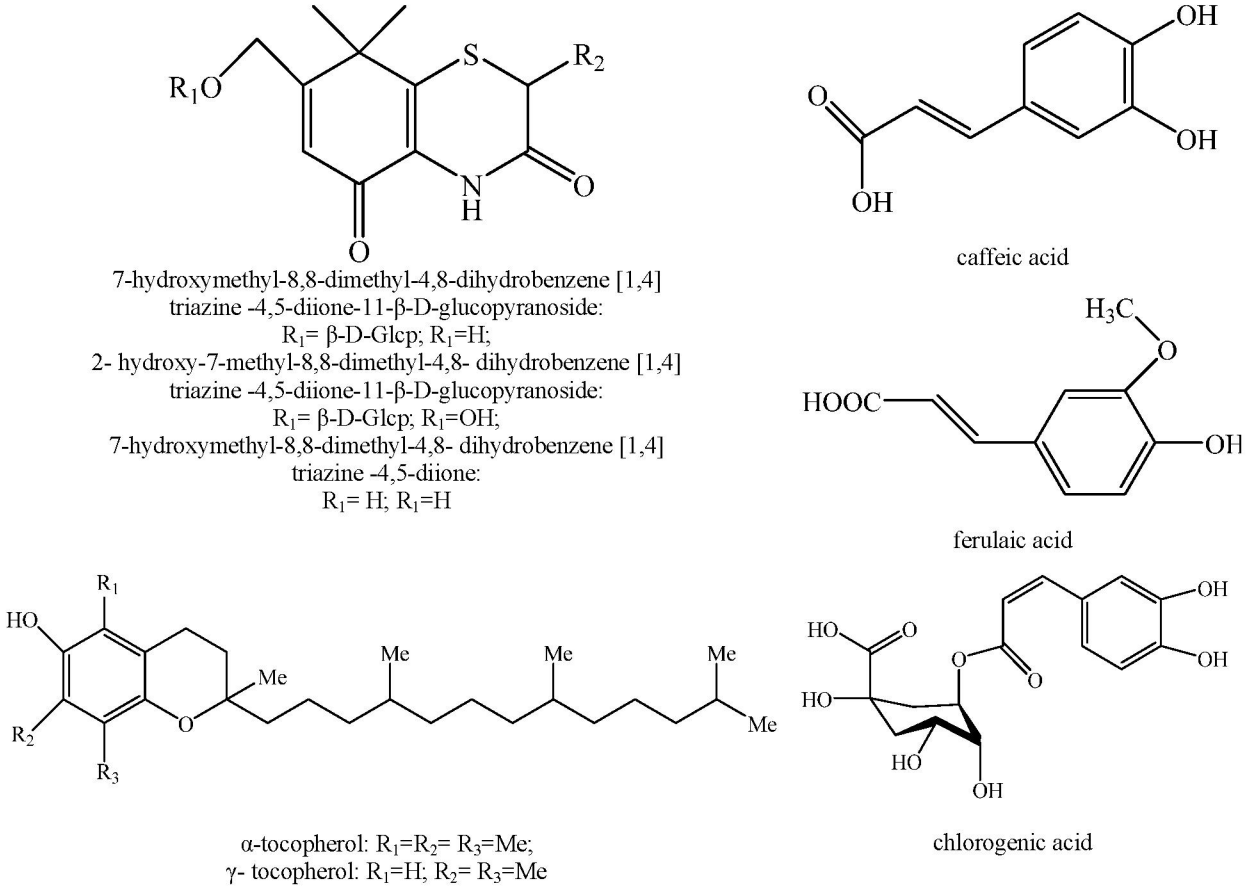
7-hydroxy-8,8-dimethyl-4,8-dihydroxybenzene [1,4] triazine-3,5-diion-(2-O-caffeol)-β-D- glucopyranoside



Anthraglycoside
M=H, R=H
carboxy anthraglycoside
M=H, R=COOH



11α-13-dihydroxy xanthatin



Structural formulas of the most important biologically active substances of *Xanthium strumarium L.*

Extraction was carried out twice at 70-80 °C for 1.5-2 hours. Obtained extracts were pooled, allowed to stand and filtered.

Assay of iodine content in the extract of *Xanthium strumarium L.* has been determined according to the procedure specified in the monograph "Laminaria[N]" of the State Pharmacopoeia of Ukraine (SPhU). This procedure involves alkaline mineralization of the raw material followed by titrimetric determination of total iodine (titrant is a 0.01 M sodium thiosulphate, indicator is a starch) [13]. This procedure was adapted to the monograph "Kelp" of the European Pharmacopoeia [14].

Investigation of thyrotropic activity of the *Xanthium strumarium L.* extract was conducted at the Central Research Laboratory (CRL) of National University of Pharmacy under the supervision of PharmDr., Prof. Yakovleva L.V. and specialist of 3 category Babenko D.I.

Study of the effect of *Xanthium strumarium L.* extract on the thyroid hormone levels and mass coefficient has been done on the mongrel female rats (body weight is 200±20 g). Rats were grown in the vivarium of CRL and were kept in the room for analysis for 7 days to adapt to environment. Throughout the study, animals were kept in natural light conditions and an ambient temperature 20±2°C. The animals had free access to food and water [15]. The animals were treated in accordance with the rules of European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes [16]. The animals were randomly divided to 4 groups (n=6/each) consisting:

1 group – intact control (IC) – healthy animals, 2 group – control of pathology (CP) – animal modeling of hyperthyroidism, 3 group – animas were intragastrically received *Xanthium strumarium L.* aqueous extract in daily manner for 20 days at the development of hypothyroidism, 4 group – animas were intragastrically received *Xanthium strumarium L.* aqueous extract in daily manner for 30 days at the development of hypothyroidism. Dose of the extract was calculated in accordance with the content of organic and inorganic forms of iodine on dried extract base and it was 1.14 g/kg equivalent to iodine content 23.92 μg/kg (it was recalculated for rats with recommended dose of iodine (400 μg/kg) for

hypothyroidism treatment) [17]. Nonclassical model of sodium perchlorate-induced hypothyroidism was chosen for the determination of thyrotropic activity of the extract. Reasonability of selected model is explained by the fact that sodium perchlorate is a competitive inhibitor of the sodium–iodide symporter (NIS) at the entrance of iodide into the thyroid and causes local iodine-deficient condition. That's why we are of the opinion that this model is suitable for study of iodine-containing medicinal products [18, 19]. Modeling of hypothyrosis was performed by the injection of 1% sodium perchlorate solution in rats for 20 days.

"Iodomarin® 100" was taken as reference drug. The investigation of the effect of the reference drug was carried out in 3 weeks after the start of first experiment with *Xanthium strumarium L.* aqueous extract. Study design and doses of "Iodomarin® 100" were the same as for study with *Xanthium strumarium L.* extract. Since animal management (temperature and light conditions, feed) was not changed and animals were grown in the same vivarium, it makes most sense to compare data of both experiments.

Animals were narcotized by chloroform, eliminated thyroids, and collected blood for serum preparation. Eliminated thyroids were weighted and mass coefficient (MC) was calculated using the following formula:

$$MC = \frac{M_{org(g)}}{M_{animal\ body\ weigh(g)}} \cdot 100.$$

Once this is done, thyroids were selected for histological examination. Levels of triiodothyronine (T3) and thyroxine (T4) were determined using the Thyroid-IFA reagent kits (Manufactured by Alkor Bio, Russia). Statistical data processing was performed using the STATISTICA 6.0 software package. The statistical significance of differences in quantitative parameters with a distribution that differs from the normal one was evaluated using Kruskal-Wallis test and the Mann-Whitney method.

Results and discussion. Obtained *Xanthium strumarium L.* aqueous extract was a brown transparent extract with a characteristic apple smell and bitter taste. It was complied with the requirements of SPhU. Determined total iodine content was 0.021 %.

The results of pharmacological study showed that T_3 and T_4 hormone levels in serum have been significantly decreased after the injection of 1% sodium perchlorate solution. That was in agreement with data obtained by other authors and gave evidence of goiter development [19]. Taking into account the significant increase in the values of the MC by 3 times in the group of control pathology compared to intact group, it can be concluded that hypothyroid condition complicated with goitrous hyperplasia develops in the experimental animals. Administration of *Xanthium strumarium L.* extract for 20 or 30 days did not increase significantly T_3 or T_4 concentration in rat blood serum despite of increased level of T_3. Increased values of T_3 concentration were not statistically significant. Significant increase in T_3 and T_4 concentration in rat blood serum was observed during the treatment with "Iodomarin®100" for 20 days. Additionally, further normalization of thyroid-stimulating hormone levels in the serum was seen at prolonged treatment (30 days) (tables 1 and 2).

Table 1 – Concentration of free triiodothyronine (T3)
in the serum of rats after administration of *Xanthium strumarium L.* extract

T_3 level (nmol/l)			
IC	CP	20-th day of administration	30-th day of administration
1.72±0.10	0.67±0.10*	0.85±0.14*	0.91±0.09*
T_4 level (nmol/l)			
IC	CP	20-th day of administration	30-th day of administration
43.83±9.82	14.1±3.6*	14.08±4.4*	13.3±4.5*

Note. 1. * – statistically significant difference compared to group of intact control; ** – statistically significant difference compared to group of control pathology, $p \leq 0.05$.
2. All data were presented as Mean±SE.

Table 2 – Concentration of free thyroxine (T4)
in the serum of rats after administration of *Xanthium strumarium L.* extract

T_3 level (nmol/l)			
IC	CP	20-th day of administration	30-th day of administration
1.27±0.21	0.59±0.04*	0.82±0.06*/**	1.20±0.20**
T_4 level (nmol/l)			
IC	CP	20-th day of administration	30-th day of administration
53.0±3.34	9.72±1.34*	14.2±2.05*/**	29.8±8.86**

Note. 1. * – statistically significant difference compared to group of intact control; ** – statistically significant difference compared to group of control pathology, p≤0.05.
2. All data were presented as Mean±SE.

Table 3 – Values of thyroid mass coefficient in rats after administration of "Iodomarin®100"

The value of MC				
Test drug	IC	CP	20-th day of administration	30-th day of administration
Xanthium strumarium L. extract	5.2	22.23*	19.7*	22.67*
Iodomarin	5.3	21.42*	21.64*	12.73*/**

Note. 1. * – statistically significant difference compared to group of intact control; ** – statistically significant difference compared to group of control pathology, p≤0.05.
2. Data is given as M±S.E.

In regard to change in MC of thyroid gland *Xanthium strumarium L.* extract did not show therapeutic efficacy at both treatment periods while "Iodomarin®100" significantly decreased values of MC by 2 times for 30 days of treatment (table 3).

Conclusion. Extract of *Xanthium strumarium L.* was obtained. Determination of total iodine was performed by the titrimetric method in accordance with the procedure set out in the monograph "Laminaria [N]"of the SphU, it was 0.021 %, respectively.

Effect of the *Xanthium strumarium L.* extract on the thyroid-stimulating hormone levels and mass coefficient was investigated on the model of perchlorate-induced hypothyroidism. It has been established that *Xanthium strumarium L.* extract exhibited inferior efficiency for normalization of thyroid-stimulating hormone levels and decrease mass coefficient of thyroid glands compared to "Iodomarin®100". Taking into account mechanism of action of perchlorate, it may be assumed that inorganic iodine contained in the tablets of "Iodomarin®100" penetrated better into the tissues of thyroid gland by contrast to other mostly organic forms of iodine in the *Xanthium strumarium L.* extract thus reducing signs of pathology and improving local iodine-deficient condition.

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САРЫСОЯУ СЫҒЫНДЫСЫНЫҢ ТИРЕОТРОПТЫ ГОРМОНДАР ДЕҢГЕЙІНЕ ӘСЕРІН ЗЕРТТЕУ ЖӘНЕ ЕГЕУҚҰЙРЫҚТАРДЫҢ ҚАЛҚАНША БЕЗІНІҢ МАССАЛЫҚ КОЭФФИЦИЕНТІ

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ИССЛЕДОВАНИЕ ВЛИЯНИЯ ЭКСТРАКТА ДУРНИШНИКА НА УРОВЕНЬ ТИРЕОТРОПНЫХ ГОРМОНОВ И МАССОВЫЙ КОЭФФИЦИЕНТ ЩИТОВИДНОЙ ЖЕЛЕЗЫ У КРЫС

Аннотация. Йододефицитные заболевания представляют собой патологические состояния, обусловленные сниженным потреблением йода. Эта группа заболеваний включает йододефицитный гипотиреоз, диффузный нетоксический зоб, узловой и многоузловой эутиреоидный зоб, функциональную автономию щитовидной железы. Наиболее часто наблюдается увеличение в размерах щитовидной железы – зоба. Эти заболевания обусловлены снижением функциональной активности щитовидной железы в ответ на дефицит йода. Очевидно, что наиболее неблагоприятные последствия возникают на ранних этапах формирования организма, начиная с внутриутробного периода и заканчивая возрастом полового созревания. Основной этиологический фактор данной патологии – дефицит йода в биосфере – практически неизменный, поэтому профилактика йододефицитных заболеваний и контроль за йодным обеспечением населения в регионах с йододефицитом является актуальной медико-социальной проблемой.

Известно, что природными источниками йода для организма являются морские водоросли, моллюски и морская рыба. Другие пищевые продукты содержат, как правило, небольшое количество этого микроэлемента. Богатые йодом бурые водоросли стимулируют щитовидную железу и регулируют метаболизм. Кроме морских водорослей и морепродуктов, для фармакологической коррекции и профилактики возникновения йододефицитных заболеваний существуют и другие растения, которые являются источниками йода и содержат вещества, действуют не на тироциты, а на клетки иммунной системы, имеющиеся в железе и ответственные за процессы тканевой регуляции. К таким растениям, которые влияют на звенья этиопатогенеза заболеваний относится дурнишник обыкновенный, который и стал объектом нашего исследования.

Получен дурнишника травы экстракт и определено количественное содержание общего йода титриметрическим методом (титрант – 0,01 М раствор натрия тиосульфата, индикатор – крахмал) по методике, приведенной в ГФУ монография «Ламинария^{N}», которое составляло 0,021 %.

Исследовано влияние дурнишника экстракта на показатели содержания гормонов щитовидной железы в сыворотке и массовый коэффициент на модели перхлорат-индуцированного гипотиреоза у крыс. Установлено, что дурнишника экстракт уступал по своей эффективности препарату сравнения «Йодомарин ®100» в способности нормализовать уровень тиреотропного гормона и уменьшать массовый коэффициент щитовидной железы. Учитывая механизм действия перхлората натрия, можно предположить, что неорганический йодид, который содержится в таблетках «Йодомарин ®100» имел большую способность к проникновению в ткани щитовидной железы по сравнению с другими, в основном органическими формами йода, содержащиеся в дурнишнике экстракте, тем самым снижая локальное йододефицитное состояние и уменьшая признаки патологии.

Ключевые слова: йододефицитные заболевания, Xanthium strumarium L., экстракт, тиреотропное действие.

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