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INFLUENCE OF ENERGY DRINKS ON INDIVIDUAL SYSTEMS OF THE HUMAN BODY

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Annotation. In recent years, energy drinks have been progressively conquering not only the market of European and Western countries, but they have also conquered the market of Asian countries. Therefore, WHO believes that the risk of such mass consumption of energy drinks among adolescents and young people can lead to serious public health problems and negative health complications in the future. Moreover, this condition is largely ignored by scientists and the public.

This rapid proliferation of new energy drinks with different names among the younger generation raises a strong concern for the scientific community in terms of their safety. There are reports in the media about a sharp loss of health and even death when drinking energy drinks with a high concentration of caffeine, alcohol-containing and after mixing them with alcohol.

Purpose: This work is devoted to the study of the influence of energy drinks on human behavior and health.

Energy drink manufacturers claim that their product contains natural ingredients that increase energy, focus, concentration and are harmless to health. At the same time, the medical community around the world is concerned about the adverse effects associated with the use, especially excessive, of "energy drinks", which are increasingly being recorded [2].

All energy drinks consist of components known to medicine, especially since they all contain caffeine, which can be found in the literature on their manufacture. It can also be obtained chemically from uric acid or by methylation of theobromine. Most often, manufacturers use synthetic, cheaper caffeine in the preparation of energy drinks. Another component of energy drinks is taurine. Sometimes they add an extract of the leaves of mate, damiana, magnolia vine, ginseng [1].

Energy drinks also contain vitamins that are related to the energy metabolism of the body, these are B vitamins, ascorbic acid, niacin. From this side, the appointment of energy drinks is not bad, in the sense that it increases energy metabolism, the vitality of the body, and this succeeds by about 20-30% [3]. The daily allowable dose of caffeine for the body is less than 150 mg, and in energy drinks their dose is from 150 to 320 mg / l. Considering that young people most often consume more than one can of energy drinks per day, and drinks are produced in cans of 250 ml or more, the latter indicates a detrimental effect on the health of people, especially adolescents, pregnant and lactating women, people with diseases of the nervous, cardiovascular systems, hypertension and other diseases with the abuse of energy drinks.

Taurine is a synthetic analogue of caffeine. It is cheaper and most often added to energy drinks in large quantities by manufacturers. The caffeine-like taurine improves energy processes, but the safety of taurine in adolescents has not been established, meaning early or late adverse reactions and effects on metabolism are unpredictable. Medical specialists have recently been increasingly talking about the detrimental effect of tonic drinks on people's health. They only managed to achieve the writing of warning labels on the packages. There is data from researchers on the relationship between the intake of energy drinks and weak alcoholic beverages and addiction to alcohol and drugs [4].

According to the Australian Poison Control Center over the last 7 years (2011-2018), the most common symptoms following energy drink abuse were palpitations, nervous agitation, tremors in the extremities, and gastrointestinal disorders [5]. Between 2000 and 2012, the US Centers for Poison Control reported 5103 cases of negative effects of energy drinks on the body, including: 552 deterioration in general well-being, 1 death, 24 serious and 527 moderate disorders of the cardiovascular system. It is important to note that 44.7% of cases occurred in children under 16 years of age [6]. From 2004 to 2012, the American Food and Drug Administration (FDA) U.S. Food and Drug Administration documented 166 cases of side effects associated with the use of energy drinks, including 18 deaths [6]. It is noteworthy that reports describe only cases of side effects of energy drinks, but there is no data on the amount of

energy drinks consumed in each case [7]. The greatest number of side effects from the use of energy drinks are observed in the cardiovascular and nervous systems, and to a lesser extent in the digestive systems and kidneys [8].

The effect of energy drinks on the cardiovascular system.

Energy drinks (EN) are gaining popularity every year with a wide range of consumers, including athletes, recreational athletes, and even those who experience work-related fatigue difficulties. Evidence suggests that a significant number of energy drink users resulting in morbidity or mortality are adolescents or young adults. Side effects of energy drinks can occur in healthy individuals, but some people may be particularly susceptible to complications. Risk groups include young people who do not drink caffeine or are sensitive to caffeine, pregnant women, competitive athletes, and those with underlying cardiovascular disease.

This part summarizes the cardiovascular complications associated with the use of energy drinks and provides suggestions for the consumption of these drinks in various populations [9].

The negative consequences for the cardiovascular system when using energy drinks are associated with the presence of caffeine in their composition. It is widely known that the use of caffeine, especially in large doses, increases blood pressure, accelerates cardiac activity and can cause arrhythmia. Caffeine enhances cardiac activity, makes myocardial contraction intense and rapid [23].

Increased blood pressure. Numerous studies have linked energy drinks and their ingredients to acute hypertension [10,11]. This is in line with known hemodynamic changes induced by caffeine intake [12,13]. Acute caffeine intake can increase plasma levels of renin, catecholamines, and dopamine. These substances stimulate the central nervous system, thereby increasing blood pressure and heart rate [14,15]. In addition, synergistic effects between the components of the "Energy Blend" used in EN may also have an effect on blood pressure [10]. The effect of caffeine on hemodynamics can last up to 5 hours after ingestion. Such effects may be enhanced by physical activity immediately after consumption [16-18].

Pulse increase. Acute consumption of energy drinks has been associated with a slight but significant increase in heart rate. Significantly prolonged QT interval in healthy young adults, as well as in individuals with pre-existing genetic long QT syndrome, which has been reported in association with EN consumption. Supraventricular arrhythmias - caffeine intake has been associated with precipitation and/or exacerbation of supraventricular arrhythmias [19]. Ventricular arrhythmias, especially ventricular tachycardia and ventricular fibrillation, which can lead to sudden cardiac death, have been associated with EN consumption [20]. It is known that caffeine increases the level of circulating catecholamines, causing hypokalemia in a dose-dependent manner. Thus, it suppresses the conduction of sodium channels, which may predispose patients to ventricular arrhythmias [10]. In addition, high doses of caffeine, such as those found in energy drinks, can exacerbate heart disease. Under such conditions, stimulants are contraindicated [21]. The most dangerous of these are ion channelopathies and hypertrophic cardiomyopathy, the most common genetic cardiomyopathy in children and young adults. These patients are at increased risk of hypertension, syncope, arrhythmias, and sudden death [21]. In addition to caffeine, taurine and guarana have proarrhythmic properties, making their consumption by patients with underlying structural heart disease potentially fatal [22].

Atrial fibrillation has been documented in the literature in a patient with dilated cardiomyopathy who developed seizures after cessation of excessive caffeine intake [24]; atrial fibrillation in a 16-year-old boy after drinking an unknown amount of Red Bull energy drink mixed with vodka [25]; atrial fibrillation in a 14-year-old athlete who drank an energy tonic after training (the volume is not known), while a similar situation occurred in him 5 days after that, but at rest [26]. Ventricular fibrillation in a young man who combined the use of "energy" with smoking marijuana was observed by Goldfarb M. et al. [27]. Cannon M.E. et al. described a fatal case of this arrhythmia in a girl with mitral valve prolapse [28], and Ward A.E. et al. diagnosed paroxysmal ventricular tachycardia in a patient with tetralogy of Fallot [29]. In addition to arrhythmias, which are the most common disorders of cardiac activity, were observed in 35% of cases [28]. With the use/abuse of energy drinks, cases of coronary spasm should also be noted [30]. Acute ST elevation myocardial infarction [31], long QT syndrome [32], aortic dissection [33], cardiac arrest [34], Takotsubo cardiomyopathy [35], postural orthostatic tachycardia syndrome [36], acute coronary thrombosis [37]. Research by Grasser E.K. et al., conducted on volunteers, showed that the use of one can of Red Bull causes an increase in systolic pressure by 10 mm Hg. Art. and diastolic by 7 mm Hg. Art., increases the heart rate by 20 beats per minute and slows down the speed of cerebral blood flow by 7 cm / s. Similar results were obtained in their studies by other scientists [38,39,40].

Energy drink consumption has been associated with several reports of adverse events, but there is limited data on associated cardiovascular complications. We describe the clinical characteristics, EN consumption profile, co-use, and cardiovascular findings in a series of reports of cardiovascular events temporally associated with EN intake from the literature. The 17 cases represents the first systematic review of the literature on acute adverse CVD events associated with EN, adding to the growing number of EN-related adverse events reported by the FDA and Health Canada. The researchers found that high EN consumption was implicated in at least 7 cases and 5 cases were associated with alcohol or other drugs. They note that in all 4 reported cases of ST elevation, the symptomatic symptom was severe chest pain. They also report that 11 cases presented with serious side effects, including cardiac arrest. Of these severe cases, most occurred either with acute severe EN intake or in combination with alcohol or other drugs. In at least

2 of these cases, there may have been an occult channelopathy that predisposes the patient to ventricular arrhythmias [41].

For the most part, the authors of the cited publications point to caffeine and taurine as the most dangerous ingredients in energy tonics in relation to the cardiovascular system, and consider an increase in platelet aggregation and endothelial dysfunction as the main pathophysiological mechanisms. There are opinions that the use of caffeine in sufficiently high doses for a long time can cause coronary heart disease, high blood pressure, and some congenital anomalies in offspring [41]. Berger and Alford (2009) similarly reported that excessive consumption of a combination of energy drinks containing caffeine and taurine causes myocardial ischemia by inducing coronary vasospasms [76]. There are several potential reasons why EN may predispose to acute adverse cardiovascular events. Caffeine in doses that can be consumed in a drink (250 mg) may lead to an increase in circulating catecholamine levels. If EN is also frequently consumed in excessive doses or rapidly, it may then lead to a catecholamine surge [41].

In 2000, a healthy, 18-year-old basketball player from Limerick, Ireland, passed out after drinking four cans of Red Bull. Before a basketball game, he died as a result of sudden death from arrhythmia syndrome. Energy drink companies. attract consumers by claiming that all synthetic ingredients are manufactured by pharmaceutical companies, which "guarantees the highest quality" of the ingredients. These companies claim a combination of caffeine, taurine, and glucuronolactone to increase energy [42].

The influence of energy drinks on the nervous system and higher nervous activity.

Excessive consumption of energy drinks containing caffeine and taurine, which are potent psychoactive substances that can modify neurotransmission, inevitably affects the functioning of the nervous system. As a result of prolonged exposure to caffeine in high doses, neuronal depletion can occur. Under the influence of caffeine, the effect of hypnotics and narcotic drugs is weakened, the reflex excitability of the spinal cord increases, and the respiratory and vasomotor centers are activated [4]. Caffeine contained in 2-3 cans of an energy drink, drunk within a short time, causes anxiety, insomnia, irritability and headaches. In acute caffeine poisoning, early symptoms of anorexia, confusion and tremors may occur. [43]. Numerous observations have shown that chronic abuse of energy tonics negatively affects the psycho-emotional state of a person. With chronic use of energy drinks under the influence of large doses of caffeine, nervousness, irritability, anger, insomnia and other adverse complications occur. Disorders of the emotional sphere, the appearance of unmotivated fear, the development of depression, sleep disorders, appetite, and an increase in the frequency of committing antisocial acts were noted. The appearance of aggressive behavior, disobedience to orders, and insomnia in conscripts after taking energy drinks was noted [44]. Abuse of energy drinks is very often combined with the use of cocaine, marijuana, amphetamines, etc., which further aggravates the situation [45]. A serious health hazard is also the mixing of energy tonics with alcohol. A feature of such a “cocktail” is a later moment of onset of intoxication, which can lead to an increase in the amount of alcohol consumed and, as a result, the emergence of alcohol dependence [44, 46]. Numerous facts of exacerbation of psychiatric diseases in people who have abused energy tonics have been documented [48-56]. In a number of cases, their use by patients suffering from epilepsy provoked the development of seizures [39-51], including, in one case, against the background of a two-year absence from them. Machado-Vieira R. et al. described the development of a manic episode in a 36-year-old patient suffering from bipolar disorder after drinking three cans of Red Bull per night [53]. Cerimele J.M. et al. stated the development of acute psychosis in a patient with schizophrenia [48]. The danger of excessive consumption of energy drinks by healthy people in the context of psychiatric pathology is confirmed by the following facts. Iyadurai S.J., Chung S.S. documented an episode of seizures without a history of epilepsy [52]. And Goruglu Y. et al. described a case of acute psychosis in a young man who had not previously had a psychiatric history [47].Taurine may be involved in interactions with the GABAergic, glycinergic, cholinergic, and adrenergic neurotransmitter systems. Caffeine is widely known to block adenosine. receptors and thereby increases the concentration of cAMP. This blockade can free cholinergic neurons from inhibitory control, leading to pervasive excitatory responses. Experimental studies with the rat show that sodium- and chloride-dependent taurine transporters exist in the blood-brain barrier. The activity of these transporters is tightly regulated by the transcription of the genes encoding them. This transcription seems to depend on the degree of cell damage, osmolality, and taurine content in the brain, suggesting that active expression of this gene is an acute response to a neuronal crisis [42].

The effect of energy drinks on the gastrointestinal tract

The most sensitive organ of the digestive system to excessive consumption of energy drinks is the liver. The first cases of liver damage from energy drinks were reported in the scientific literature in 2011. Thus, Vivekanandarajah A. et al. described a case of acute hepatitis in a 22-year-old girl who consumed about 10 cans of a drink per day for two weeks (trade name not specified) [56]. In the same year, Apestegui C.A. et al. described a case of cholestatic hepatitis in a liver transplant patient who drank 15 cans of Red Bull over three days [57]. In both cases, the authors of the cited publications associated the hepatotoxicity of drinks with a high content of vitamin B3 in them. [58]. A similar clinical situation was reported by Harb J.N. and others [57]. A 50-year-old man who consumed 4-5 cans of energy drink (brand not specified) per day for 3 weeks showed signs of acute hepatitis: an increase in the level of aminotransferases and direct bilirubin in the blood; increased liver echogenicity and diffuse thickening of the gallbladder wall on ultrasound; bridging necrosis and severe cholestasis in the biopsy material [59]. In contrast to previous episodes, Huang B. et al.

reported a case of severe liver damage in a 36-year-old man who drank three cans a day of Rockstar energy drinks for 1 year while drinking heavily. In this situation, conservative treatment was ineffective, and the patient underwent orthotopic liver transplantation. The authors of the cited publications attribute the hepatotoxicity of energy drinks to the vitamin B3 they contain (vitamin PP, nicotinic acid or niacin), which exhibits hepatoprotective properties in small doses, and in excess has a direct toxic effect on the liver tissue [42].

Taurine biosynthesis occurs in the liver via the cysteine sulfinic acid pathway. The average human intake is estimated to be around 60 mg per day. Premature babies lack the enzyme that converts cystine and synthesizes taurine, and taurine deficiency may occur. Therefore, for the preterm infant, taurine is a dietary essential nutrient often found as an additive in infant formulas and infant formulas [61]. Some countries (France, Denmark, and Norway) initially banned energy drinks due to their taurine content, but based on evidence to date, taurine consumption is safe to consume [62,63]. Energy drinks have potential side effects attributed to the presence of caffeine. It has been found that large doses of caffeine (3 mg/kg) can lead to health problems such as impaired glucose tolerance, gastrointestinal irritation, anxiety, irritability, nausea and tachycardia, and the dose of caffeine should be reduced [61,64]. Most energy drinks are considered harmful to the human body; therefore, these drinks should be closely monitored due to the imbalanced composition of ingredients, especially sugar and caffeine in their composition [65]. People drink Red Bull to get the energy to perform activities, relieve fatigue from a workout, or perform work duties. The general public should not consume energy drinks during exercise as the combination of all stimulants and other ingredients in energy drinks can lead to fluid loss due to sweating and cause severe dehydration and serious health problems [66, 67]. As a result of an experimental study of the effect of Red Bull on major critical organs such as the kidneys, liver, heart and brain, we can conclude that energy drinks have a dose-dependent relationship to adverse reactive effects. This makes it possible to conclude that the consumption of these energy drinks can seriously harm the body [60].

In addition, energy drinks can cause hyperinsulinemia and a decrease in tissue sensitivity to insulin by about 30% [49, 50].

In the world of scientific data concerning research on the histopathological effect of Red Bull on the stomach and duodenum, relatively few are available. Scientists have studied the histopathological effect of Red Bull consumption on the gastric and duodenal mucosa of male rats. They were housed in standard environmental conditions with free access to standard tableted rat food and free tap water. The study was conducted in accordance with research ethics norms established by the guidelines for the care and use of laboratory animals. All animals were housed in suitable plastic cages at a controlled temperature (25 ± 2 C°) with a fixed 12 h light-dark cycle for one week prior to the start of the acclimatization experiment [72].

Thirty animals were randomly assigned to 2 groups of 15 rats each. In group I (control group): the animals were given distilled water using an oropharyngeal metal bent tube at a daily dose of 1.071 ml/100 g body weight (B.W.) for three months. Group II (Red Bull group): Animals were given Red Bull using an oropharyngeal metal bent tube at a daily dose of 1.071 ml/100 g for three months (Ferreira et al., 2004). At the end of the experiment, all animals were euthanized. The stomach and duodenum were excised and processed for histological and immunohistochemical studies [72]. The excised stomach is opened, cleaned and photographed to show macroscopic changes in its mucosa. The duodenum was washed with saline. Cleaned up the inside. The stomach and duodenum were fixed in 10% buffered formalin at 4°C for 48 hours. and embedded in paraffin. Sections were stained with hematoxylin and eosin (HandE) and periodically with Acid Schiff (PAS).

The study data shows depletion of gastric and duodenal secretions in the Red Bull group, as evidenced by the marked depletion of PAS-positive material. This could be due to massive damage to the mucous membrane and detachment of epithelial cells. The results were in agreement with Nawrot et al. (2003), who also reported that the inhibitory effect of caffeine on gastric mucus secretion may be one of the important factors in gastric mucosal injury. The results of the present study demonstrated a significant increase in the number of apoptotic cells, as evidenced by a significant increase in caspase-3-immunopositive cells of the gastric and duodenal mucosa of the Red Bull group [72]. Previous studies have shown histopathological lesions in various organs, including pancreas and gastric fundus (Ayuob, ElBeshbeishy, 2016), liver (Khayyat et al., 2012), submandibular salivary gland (Mubarak, 2012). Ayouob and El Beshbeishi (2016) recently evaluated the structural effect of the pancreas and gastric fundus mucosa in adult male albino rats by drinking one of the Power Horse energy drinks for 4 weeks. Their results showed degenerative histopathological changes in the fundus of the gastric mucosa with a reduced number of parietal cells. They explain that these changes are induced by caffeine, with an increase in the levels of tumor necrosis factor alpha (TNF-α) and inducible nitric oxide synthase (iNOS), which led to an imbalance of oxidants/antioxidants in these tissues and increased oxidative stress [69]. Another study showed that caffeine significantly potentiated aspirin-induced damage to the rat gastric mucosa for 3 weeks [70]. Caffeine is considered a moderately strong stimulant of gastric acid secretion in dogs and humans (Cook, 1976). Stimulates the secretion of gastrin and secretion of gastric juice. It also prolongs adaptive relaxation of the proximal stomach, and slows gastric emptying [77]. This, in turn, can increase the duration of direct exposure of Red Bull to the gastric mucosa and cause macroscopic and microscopic changes in the gastric mucosa. Other studies point to oxidative stress-induced apoptosis of gastric epithelial cells and pancreatic acinar cells [69]. Huxtable (1992) suggested an additive effect of taurine to that of caffeine on the gastric and duodenal mucosa. He reported that taurine conjugates with bile acids and aids in the digestion of lipids, including cell membrane lipids. This may explain the noted association. Apoptosis is observed in the mucosa of both the stomach and the duodenum. In

addition, there is evidence for other ingredients in energy drinks. Sodium benzoate is thought to be the cause of cellular necrosis in rats following excessive consumption of Red Bull [71]. An analysis of literature data with a great deal of convincing evidence that excessive consumption of energy drinks can have an extremely adverse effect on human health and can lead to the development of multiple organ failure, with damage, primarily to the cardiovascular, central nervous systems, as well as the liver and kidneys. To substantiate indications and contraindications, recommendations for the use (volumes and dosages) of energy tonics, it is necessary to obtain a clear evidence base based on complex clinical, laboratory, instrumental, and experimental morphological studies [42].

It can be concluded that energy drinks have many harmful side effects due to the presence of many ingredients, while the side effects of each ingredient are not severe enough to be banned [60].

Urinary system

Another target organ for the action of energy drinks is the kidneys, because. cases of acute renal failure have been reported in individuals, often and in large quantities, taking drinks of this category [73, 74].

Akande and Banjoko (2011) reported an increase in urea concentration in rats after excessive consumption of energy drinks. They explained this increase by caffeine through inhibition of A2 adenosine receptors, which in turn accelerates the development of interstitial inflammation, exacerbates proteinuria, and alters the function and structure of the kidneys [76]. Tofovich et al. (2002) reported that caffeine caused severe tubulointerstitial damage in rats, including tubular atrophy, proteinaceous material, tubular dilatations, interstitial inflammation and interstitial fibrosis, and increased glomerulosclerosis [78].

Shimizu et al. (1996) attribute renal tubular and glomerular necrosis as a consequence of ATP depletion from energy drinks, which ultimately leads to cell death [79].

Red Bull has been known as a healthy drink for many populations. The chemical composition of energy drinks can cause multiple side effects, including serious behavioral effects. To study the effects of energy drinks (Red Bull) on the brain, liver, kidneys, and heart in rabbits, the researchers used thirty male albino rabbits, and the animals were divided into 3 groups (A, B, and C) of 10 rabbits. Group A received a high dose of Red Bull (10 ml), group B received a low dose (5 ml) and group C was the control. The results showed that there were no pathological changes in the control group, while there were many pathological changes in both groups A and B. Changes in group A showed renal vascular congestion, interstitial tissue hemorrhage, focal atrophy and degeneration of the epithelial lining in the proximal and distal convoluted tubules, while group B showed renal vascular congestion, glomerular capillary congestion, interstitial tissue hemorrhage with swelling of the lining epithelium of the proximal and distal convoluted tubules, swelling of the glomeruli. This shows that there is a dose-response relationship between the low and high dose Red Bull groups. It can be concluded that energy drinks have a dose-dependent effect with side effects. It became apparent that the consumption of these energy drinks seriously harms the body [60].

Influence of energy drinks on the morphofunctional state of stress-organizing endocrine glands

To study the effect of energy drinks on the pineal, pituitary and adrenal glands, scientists conducted an experiment on 20 adult rats divided into 2 groups: experimental (n = 10) and control (n = 10). Rats from the experimental group were orally administered a caffeinated energy drink of a well-known brand once a day at a dose of 6 ml per 1 kg of body weight for two weeks. The control group consisted of healthy intact animals.

The pineal, pituitary, and adrenal glands of experimental animals were fixed in 10% neutral formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin and Einarsson'sgallocyanine chromic alum. Immediately after the decapitation, blood was taken. The content of catecholamines and serotonin in the blood serum was determined using the method of spectrofluorimetry [80]. When studying the morphofunctional state of the epiphysis, the posterior pituitary gland and the adrenal medulla, as well as the presence of serotonin and catecholamines in the blood serum of rats during the experimental administration of energy drinks, scientists found an increase in the content of serotonin, norepinephrine and adrenaline in the blood serum. The morphofunctional state of the above endocrine glands was sharply stimulated. Indirect signs of apoptosis of parenchymal cells in the pineal gland, neurohypophysis, and adrenal medulla were determined; stimulation of hormone production (serotonin, norepinephrine, adrenaline, vasopressin) was noted [81]. Our review of the literature shows that although energy drinks lead to all of these unexpected histopathological changes, the popularity of energy drink consumption continues to grow. Energy drinks can produce different effects due to the different combinations of their ingredients. Therefore, more research is recommended on different types of energy drinks and their possible specific adverse histopathological effects on various tissues and organs. Regarding the limitations of the study, the authors did not test the reversibility of histopathological effects on the stomach and duodenal mucosa and did not test their effects on serum levels of gastrointestinal hormones. It can be said that massive histopathological changes in the gastric and duodenal mucosa were the result of excessive consumption of the Red Bull energy drink for a long time. Caffeine has been the most blamed ingredient for these effects, although other ingredients such as taurine, sodium benzoate, and ascorbic acid may be involved. These results will be the reason for further investigation of the histopathological effect of energy drinks on other organs of the digestive tract: the jejunum, ileum, and colon. Research on the optimal dosage of intake, as well as on the reversibility of effects in case of excessive intake, will also be important.

Conclusions: An analysis of literature data with a high degree of persuasive evidence that excessive consumption of energy drinks can have an extremely adverse effect on human health and can lead to the development of multiple organ failure, with damage, first of all, to the cardiovascular, central nervous, endocrine systems, as well as the digestive and excretory systems. To substantiate the indications and contraindications, recommendations for the use (volumes and dosages) of energy drinks, it is necessary to obtain a clear evidence base based on complex clinical, laboratory, instrumental and experimental morphological studies.

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