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THEORETICAL JUSTIFICATION OF THE CHOICE OF MEDICINAL PLANT RAW MATERIALS FOR THE CREATION OF A HERBAL TEA INTENDED FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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The incidence of diabetes mellitus of the second type is growing every year, and the search for medicines for supporting therapy of patients is urgent. Ideally, the treatment program should include exposure in several directions: to have hypoglycemic, hypolipidemic effects, to prevent the progression of vascular complications, etc. The fact is that the medicines having only a hypoglycemic effect are not able to prevent the development of complications and normalize metabolism in patients with diabetes mellitus. The article highlights the issues related to the state of morbidity of the population with diabetes mellitus. A conceptual model of maintaining glucose homeostasis during and after meals, proposed by Mukhamedzhanov E.K., is presented. The characteristics of plants and the mechanism of action of biologically active substances (BAS) that contribute to a complex effect on the pathological process in the treatment of type 2 diabetes mellitus are given. Among them there are roots and rhizomes of elecampane inula, sunflower family (Inula helenium L., Asteraceae family), that are rich in inulin, which can be used as a prebiotic to modulate the gut microbiota, potentially affecting glucose homeostasis and lipid profile; leaves of cowberry, heath family (Vaccinium vitis-idaea L., Ericaceae family), containing tannins and arbutin, which in its individual form is currently a promising substance for the diabetic nephropathy control; dog rose fruits, Rose family (Rosa canina L., Rosaceae family) having a large set of biologically active substances (studies have shown that rosehips prevent obesity and diabetes); motherwort herb, mint family (Leonurus cardiaca L., Lamiaceae family), that is rich in flavonoids such as rutin, apigenin and others. Rutin reduces the absorption of carbohydrates from the small intestine, stimulates the secretion of insulin by beta cells, protects the islet of Langerhans from degeneration, increases the absorption of glucose by tissues and suppresses gluconeogenesis in the liver.

The expediency of using a plant composition made of the roots and rhizomes of elecampane inula, lingonberry leaves, rosehips and motherwort herb, which are sources of inulin and inulicin, arbutin, vitamin C and organic acids, rutin and apigenin, is shown.

Keywords: diabetes mellitus, mechanism of action, plant raw materials, hypoglycemic tea

A chronic disease in which the pancreas does not produce enough insulin or the body itself is unable to use it is called diabetes. In the first case, it is type 1 diabetes mellitus (DM1) and as a treatment, regular insulin is injected into the patient's body. In the second case it is type 2 diabetes mellitus (DM2).

Significantly more people suffer from type 2 diabetes than from the first one. It is often called as a "disease of civilization" because the incidence of it is growing every year [1]. According to the World Health Organization, the number of cases increased from 108 million in 1980 to 422 million in 2014, and premature mortality increased by 5% for the period from 2000 to 2016.

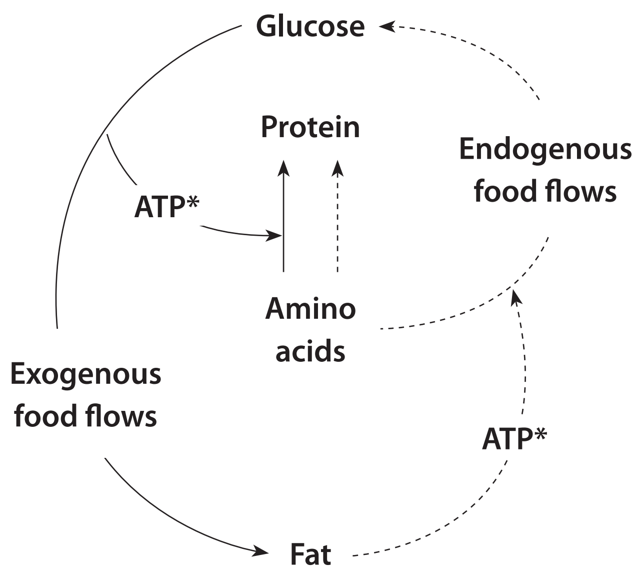
For the first time, the term "insensitivity to insulin" was introduced in 1939 by Himsworth and Kerr to define the lack of an organism's response to insulin administration in diabetic patients. Type 2 diabetes is characterized by impaired glucose tolerance, which is caused by insensitivity of cells and tissues of the body to insulin [2]. Insulin resistance can lead to a number of pathological processes. All together it is known as "insulin resistance syndrome". This syndrome includes the following disorders: obesity, increased triglyceride levels, arterial hypertension, impaired fasting glycemia, increased levels of thrombic and antifibrinolytic factors, impaired glucose tolerance. All this can eventually lead to cardiovascular diseases [3].

One of the most popular ways to manage DM2 is to reduce glycemia. Glucose homeostasis can be maintained by autoregulation of enzymes responsible for glucose breakdown, but such regulation has limited possibilities. In the case when enzymes fail to cope with the specified task, complex mechanisms for maintaining glucose homeostasis are activated. A conceptual model of maintaining glucose homeostasis during and after meals was proposed by the scientist Mukhamedzhanov E.K. (Fig. 1) [4].

Glucose is a source of energy for the brain and blood cells. Proteins act as a coordinator of carbohydrate and fat metabolism when using exogenous and endogenous food flows. Excess exogenous food flows are converted into fats. Glucose catabolism consumes ATP energy for protein synthesis. That is, with a decrease in carbohydrates in the diet, the amount of energy that is released for protein synthesis decreases. If, on the contrary, the food is relatively poor in protein and excessively rich in carbohydrates, then protein synthesis decreases due to insufficient substrate support, as a result of which less ATP is released for protein biosynthesis and the formation of ATP in the system is reduced in principle.

Inhibition of glucose uptake leads to its accumulation in the blood, which, in turn, forces the pancreas to secrete more insulin, as a result of which the discharge of the carbon skeleton of glucose into fats accelerates and hyperlipidemia develops.

In the Russian Federation, the tactics of managing a patient with diabetes mellitus were specified in the Consensus of the Council of experts of the Russian Association of Endocrinologists on the initiation and intensification of hypoglycemic therapy [5]. Ideally, the treatment program should include effects in several directions, have hypoglycemic, hypolipidemic effects, prevent the progression of vascular complications, etc. The fact is that the medicines that have only a hypoglycemic effect are not able to prevent the development



* ATP – Adenosine triphosphate

FIG. 1. *Model of glucose homeostasis*

of complications and normalize metabolism in patients with diabetes mellitus. Based on this, it can be concluded that it is necessary to bring to the market safe and effective complex preparations for the treatment of diabetes of type 2.

Among the numerous active substances that affect the reduction of glucose tolerance, it is necessary to note substances of plant origin that have a wide spectrum of action and a complex effect on the body. In addition, they have a number of obvious advantages over synthetic molecules, for example, they have low toxicity, which allows them to be used for a long time without pronounced side effects, have a mild effect, are combined with medicinal substances, enhancing their therapeutic effect [6].

The glucose homeostasis model presented in Fig. 1 demonstrates the influence of exogenous and endogenous factors, some of which can be controlled, including in pharmacotherapy the groups of substances that contribute to the normalization of glucose uptake and transport into cells, its excretion from the body and reduction of insulin synthesis from proinsulin.

For example, S.A. Kalmykov, when developing a tea for the treatment of diabetes mellitus, proposed an algorithm for selecting medicinal plant raw materials for the tea, including [6]:

- substances that promote the activation of hexokinase, which is necessary for the phosphorylation of glucose, or substances that promote the conversion of glucose into mannose and fructose, for the uptake of which insulin is not required (for example, substances of the guanidoisoamylene group);
- substances containing chromium, which provides glucose transport to cells. It has a hypolipidemic effect, prevents the development of cardiovascular diseases;
- substances with antioxidant activity. They protect β-cells by neutralizing reactive oxygen intermediates, causing a violation in the structure of their DNA, which ultimately leads to decrease in proinsulin synthesis;
- substances that have a diuretic effect, due to which the removal of excess glucose from the body is ensured, and substances that improve the functioning of the links of the immune system.

Promising objects with the above properties, as well as having an extensive domestic raw material base, are the following plants: motherwort, mint family (*Leonurus cardiaca* L., Lamiaceae family), cowberry, heath family (*Vaccinium vitis-idaea* L., Ericaceae family), elecampane inula, sunflower family (*Inula helenium* L., Asteraceae family), dog rose fruits, rose family (*Rosa canina* L., Rosaceae family).

The roots and rhizomes of elecampane inula are rich in inulin (up to 44%), inulicin (Fig. 2), as well as polysaccharides, for example pseudo-inulin, in addition, saponins, resins, gums were found in the extracts [7].

Inulin is a fermentable indigestible carbohydrate, and its effect on the lipid profile and glucose level has been studied for a long time (8). Inulin has a long chain of polymer residues (n=10-60), which allows it to remain in the human body and have a positive effect on it for a longer time until it reaches the colon (9). In recent years, there has been more and more evidence that the gut microbiota plays a crucial role in the development of inflammation and metabolic disorders, such as obesity, insulin resistance and type 2 diabetes mellitus [10,11]. Inulin can be used as a probiotic to modulate the gut microbiota, which potentially affects glucose homeostasis and lipid profile due to the balance of satiety hormones, regulation of lipid synthesis and reduction of insulin resistance [12].

In the studies of scientists Dehgan P. and Beylot M., aimed at studying the effect of inulin on the state of people with obesity or DM2, there was a significant decrease in total plasma cholesterol during 6–8 weeks of inulin treatment compared with the control group [13,14]. In addition, the analysis of subgroups by types of insulin-type fructosans showed that the consumption of inulin alone without additives of other polysaccharides

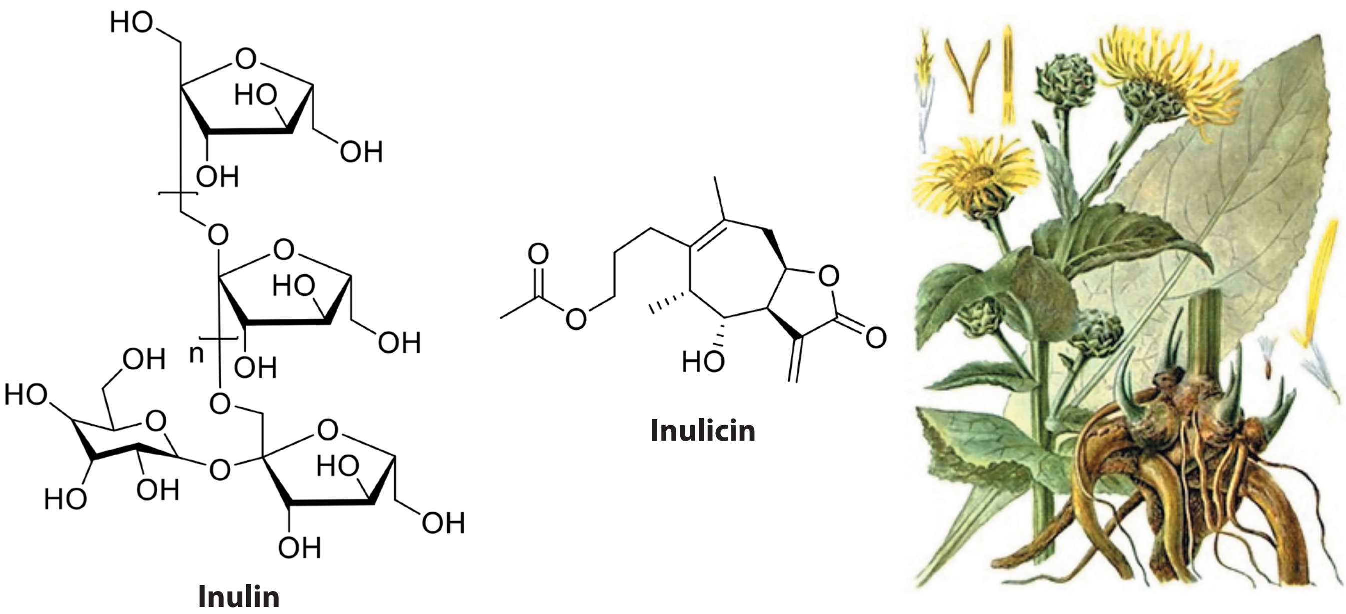


FIG. 2. *Structural formulas of inulin and inulicin and the structure of elecampane inula*

improved the lipid profile and reduced total cholesterol. The mechanism of action of inulin-type fructosans on glucose and lipid metabolism remains unclear. A number of mechanisms have been proposed concerning the effect of inulin on lowering the cholesterol levels. One of them was considered as a possible way to reduce cholesterol absorption through intestinal epithelial cells [15]. Inulin is a soluble and viscous compound that increases the thickness of the unmixed layer of the small intestine, thus inhibiting the absorption of cholesterol [16]. Inulin does not bind to bile acid in the upper digestive tract, however, it can help bile acid interact with bacteria or insoluble compounds such as calcium phosphate by lowering the pH of the cecum [17]. As a result of increased excretion of bile acids with feces, the use of cholesterol to restore bile acid in the liver increases, which, in turn, reduces the concentration of cholesterol in it

Another potential mechanism of action is that changes in the composition of the intestinal microbiota after the intake of short-chain inulin-type fructosans lead to an improvement in glucose and lipid metabolism and reduce the level of lipopolysaccharides in plasma, as shown by the example of mice [18]. In the colon, inulin is broken down by the gut microbiota into short fatty acid residues such as acetate, propionate and butyrate [19]. As a rule, propionate and butyrate are metabolized in the colon and liver, which mainly affects local intestinal and liver functions. They also cause gluconeogenesis and sympathetic activity in the intestine, which improves glucose homeostasis. In addition, circulating acetate can be absorbed by the brain and subsequently regulate the feeling of satiety through a central homeostatic mechanism [20,21]. Butyrate suppresses cholesterol synthesis in the liver by suppressing lipogenic genes in it and provides energy to epithelial cells of the human colon [22,23].

The roots and rhizomes of elecampane can serve as a source of inulin both as part of the tea and as a result of extraction.

The leaves of cowberry contain tannins and arbutin (Fig. 3) – a glycoside of the phenolic type [24].

Arbutin in its individual form is currently a promising substance for the diabetic nephropathy management. Diabetic nephropathy is a complication in patients with diabetes mellitus, which in 80% of cases leads to renal failure [25,26]. Recently, in the treatment of diabetic nephropathy,

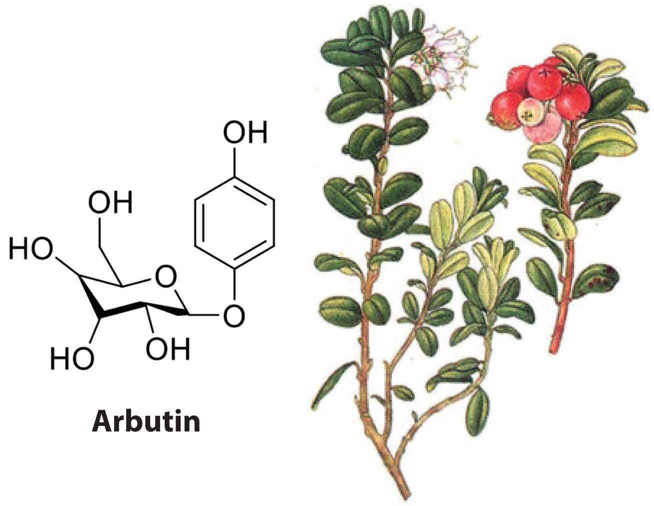


FIG. 3. *Structural formula of arbutin and the structure of cowberry*

emphasis has been placed on blood sugar control, regulation of blood lipids, diet compliance [27]. Compliance with the doctor's recommendations can slow down the development of the disease, but in the long term it still leads to unpleasant consequences. One of these consequences is tubular necrosis, i.e. the death of tubular epithelial cells forming renal tubules. Tubule damage is particularly active in an environment with high glucose content [28]. Arbutin has been shown to inhibit the apoptosis of tubular epithelial cells induced by increased glucose content.

In addition, Yuritsa K. and colleagues studied the role of arbutin in human peripheral blood lymphocytes and found that arbutin can inhibit lymphocyte proliferation [29]. In B. Zhang 's studies, the bactericidal [30], anti-inflammatory [31] and anti-glycation effects of arbutin in vitro have been confirmed.

In the work of Farzanegi and co-authors, data on the study of the effect of arbutin on the protection of cardiac tissue in experimental animals with diabetes-induced oxidative stress are presented [32]. And the antioxidant activity of arbutin can reduce the risk of DM2 by improving protection against oxidative stress [33,34].

Dog rosehips have a large set of biologically active substances. It is known for having the highest vitamin C content compared to other plants and is a source of organic acids. In addition, carotenoids, vitamins P, B1, K, E, polyphenolic substances, flavonoids, catechins, anthocyanins, tannins and chlorophylls can be found in its composition. The percentage of certain substances depends on the soil, the season and even the height of the shrub growth above sea level. Rosehips contain vitamin C, citric acid, malic acid (Fig. 4) [35,36].

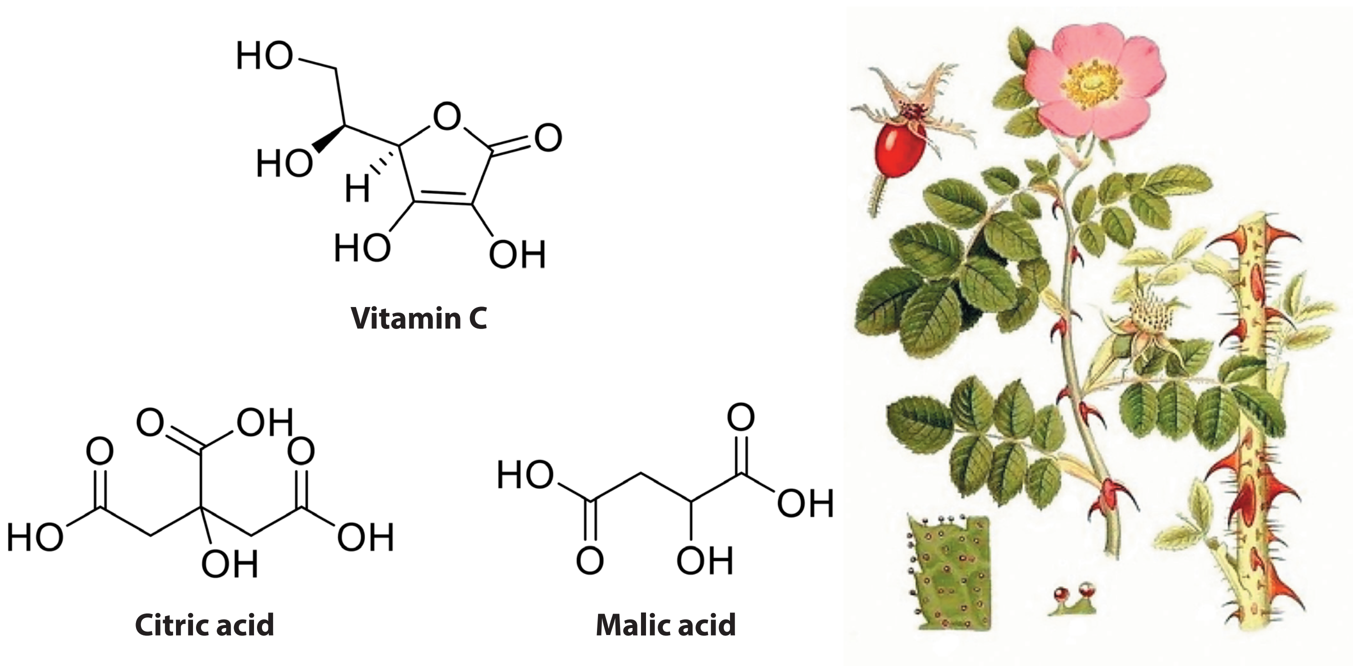


FIG. 4. *Structural formulas of vitamin C, citric acid, malic acid and the structure of rose hips*

During the last decade, the anti-inflammatory properties of rosehip have been documented in several studies, and it has been successfully used to relieve symptoms in patients suffering from osteoarthritis, rheumatoid arthritis and lumbar pain [37-41]. Two independent studies conducted on two different mouse lines have shown that rosehips prevent obesity and diabetes. In one of them [42], mice were injected with acetone extract of rosehip fruits and seeds, which helped prevent weight gain in mice that did not follow a diet. Another used a line of mice simulating obesity and human insulin resistance. During the study, they were injected with rosehip fruit powder, which made it possible to stop weight gain and reduce insulin resistance [43]. The mechanism of lowering the level of cholesterol in plasma could not be determined, there was a decrease in the level of cholesterol in both plasma and liver, although it was recorded that there was no effect on the biosynthesis of cholesterol. Afterwards, the same group of scientists provided a human subject research to study the metabolic effects of administration of rosehip (44). As a result of daily consumption of rosehip fruits, a significant decrease in cholesterol levels was observed, but unlike rats, there was no effect on body weight, glucose tolerance and markers of inflammation.

The motherwort herb is rich in flavonoids such as rutin, apigenin (Fig. 5) and others [45].

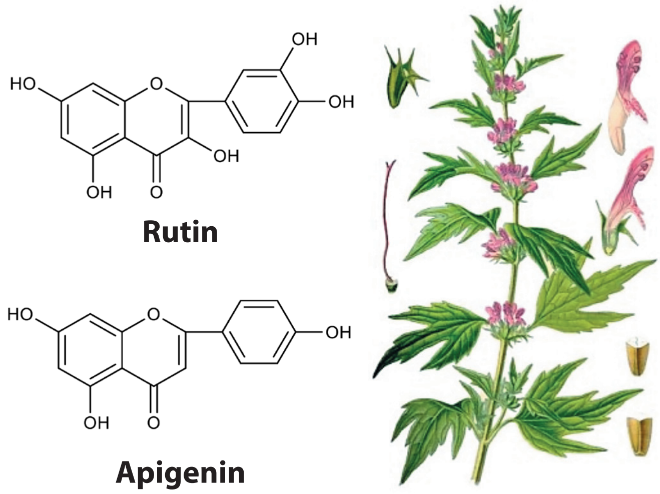


FIG. 5. *Structural formulas of rutin, apigenin and the structure of motherwort herb*

The data show that glucose transporters play a key role in the absorption of sugar, which makes them attractive targets for the discovery of antidiabetic agents [46,47]. Glucose is a hydrophilic compound and cannot pass through the lipid bilayer due to passive diffusion, therefore, specific carrier proteins are required for its transport to the cytosol. The small intestine and kidneys express several isoforms of glucose transporters, such as GLUT1, GLUT2, GLUT5 and Na+-dependent glucose transporter 1 (SGLT1). Consequently, new strategies for the prevention and treatment of diabetes and obesity can be achieved due to reducing glucose absorption by inhibiting these glucose transporters in the intestine or due to stimulating the renal glycosuria.

A research was conducted to study the effect of flavonoids on glucose transport via human SGLT1 [48]. Various subclasses of flavonoids (flavones, isoflavones, flavonols, flavanones) were studied by measuring the glucose transport in oocytes expressing the human SGLT1. As a result, apigenin showed good activity.

Diabetic cardiomyopathy is an independent ischemic heart disease that develops in diabetics, characterized by changes in the structure and function of the myocardium. It has been shown [49] that rutin protects and improves myocardial dysfunction by preventing oxidative stress, apoptosis and inflammation in the hearts of diabetic rats. Rutin can protect the liver in diabetes by alleviating inflammation, steatosis, fibrosis, as well as rutin promotes signal transmission along the insulin signaling pathway in the liver and hepatocyte proliferation [50].

Rutin reduces the absorption of carbohydrates from the small intestine, stimulates the secretion of insulin by beta cells, protects the islets of Langerhans from degeneration, increases the absorption of glucose by tissues and suppresses gluconeogenesis in the liver [51].

Rutin reduces glucose absorption from the small intestine by inhibiting α-glucosidases and α-amylases involved in the digestion of carbohydrates. Suppression of glucose absorption in the intestine prevents sharp increase in blood glucose levels after eating. Lowering blood glucose levels can also be achieved due to stimulating the insulin secretion by beta cells and increasing the glucose uptake by tissues. In isolated islets of the pancreas of rats, rutin significantly increases insulin secretion. In rat beta cells, rutin increased glucose-induced insulin secretion and maintained glucose sensitivity under conditions of high glucose levels. Rutin also showed the role of the insulin mimetic in the soleus muscle of rats and the muscles of the diaphragm. It stimulated the glucose transport into the muscles by activating the synthesis and translocation of the GLUT-4 transporter. Rutin also increases the expression of PPARy, which improves insulin resistance and glucose uptake in skeletal muscles and adipose tissue.

Histopathological studies in vitro on rats with diabetes have shown that rutin improves the histoarchitectures of the islets of Langerhans. Treatment of rats with STZ-induced diabetes with 50 mg/kg and 100 mg/kg rutin prevented a reduction in the size of the pancreas and a reduction in the number of islets. Rutin has also been shown to suppress glucolipotoxicity in rat pancreatic beta cells by activating the insulin receptor substrate-2 and signaling of AMP-activated protein kinase.

CONCLUSION

As a result of the analysis of the literature data, the expediency of the integrated use of motherwort, mint family (Leonurus cardiaca L., Lamiaceae family), cowberry, heath family (*Vaccinium Vitis-idaea* L., Ericaceae family), elecampane inula, sunflower family (*Inula helenium* L., Asteraceae family), dog rose, rose family (*Rosa canina* L., Rosaceae family) has been shown as rich sources of biologically active substances that are active participants in biochemical processes aimed at counteracting of the mechanism of the pathological process in type 2 diabetes mellitus.

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