



Herbal Infusions and Teas Taken Orally: What is not Taken into Account in the Phytotherapy of Type 2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AU, NU and LL designed the study and wrote the protocol. Authors AS, RF, AA and NK wrote the first draft of the manuscript. Authors AU and LL managed the analyses of the study. Authors DS, EG, SK and IK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Infusions, decoctions and teas made from hot drinking water and various medicinal plants are widely used in folk medicine and pharmacy in the Russian Federation and in the countries of Southwest Asia. In this study, the methods of ethnopharmacology and pharmacy were combined to clarify the mechanism of action of traditional herbal mixtures in the phytotherapy of type 2 diabetes mellitus. The technology of preparation of infusions, decoctions and teas from medicinal plants and the quality of water are analyzed. It is shown that the traditional assessment of the pharmacological activity of herbal mixtures was previously considered only from the point of view of the biological activity of the main chemical components, without taking into account the influence of water, its volume, as well as without taking into account acidic, osmotic (hypotonic) activity and temperature of water extracts. However, it has been shown that drinking water is also the main active ingredient

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of water extracts, and the quality of water and its physical-chemical properties can be important in the effect on the body of patients. In particular, attention is drawn to the fact that ingestion of 250 ml of such aqueous extracts can dilute blood plasma, reduce the concentration of all substances in it, including glucose concentration, reduce osmotic activity of the plasma and promote the removal of glucose from the body due to its "washing". Therefore, traditional herbal medicine based on ingestion of 250 ml of aqueous extracts 2-4 times a day may be accompanied by hypoglycemia and a decrease in the concentration of all other ingredients in the blood plasma not so much due to the action of biologically active substances, but also due to the action of water. The process of reducing the concentration of glucose in the blood is more intense and significant, the faster the water is absorbed into the blood and the more water is drunk. It is also obvious that some of the glucose is excreted with water from the body during urination and sweating. Nevertheless, in order to give a definitive answer to the role of herbal teas and infusions in the phytotherapy of diabetes mellitus, new and more comprehensive pharmacological studies are required in the future, taking into account the volume of water and the physico-chemical properties of water extracts.

Keywords: *Diabetes mellitus; phytotherapy; herbal preparations; herbal teas; plant infusions; volume; hypotonic activity.*

1. INTRODUCTION

Phytotherapy of various diseases is regulated by the licensing documentation of health authorities and is included in conventional medicine [1]. The basis of medicines that are used in modern phytotherapy are water extracts of flowers and stems of plants devoid of poisonous and potent compounds, therefore these infusions and teas have good tolerability and low frequency of side effects compared with synthetic drugs [2-4]. The fact is that the safety of the plants used has been confirmed by their safe ingestion by various representatives of the animal world for many millions of years. The range of biologically active compounds is particularly wide in the flowering part of plants. This is due to their role in symbiosis with bees and other pollinators. The chemicals involved in this ensemble of natural relationships include volatile compounds responsible for their odor (fatty acid derivatives, benzoids, phenylpropanoids, isoprenoids, nitrogen-containing compounds, etc.); pigments that color flowers, such as anthocyanins, flavonoids and betalains; nectars with amino acids, carbohydrates, vitamins, mineral ions, etc.; and, finally, some toxic substances, such as alkaloids, non-protein amino acids, lectins, ammonia and heavy metals [5].

Herbal mixtures form an important part in folk medicine, especially in the treatment of diseases of multi-causal etiology. Numerous herbal blends have been used for centuries and have been proven to improve health. However, the mechanism of their action is still controversial among researchers. Traditionally, it is believed that the mechanism of action of herbal

preparations is associated with the action of chemical compounds. Therefore, the active search for plants with potential hypoglycemic activity continues due to the presence of biologically active substances in them [6-9]. To date, the following plants are of great interest in Russia and in the countries of Western Asia: onion (*Allium cepa*), garlic (*Allium sativum*), pharmacy goat (*Galega officinalis L.*), iambolan (*Syzygium cumini*), momordica charantia (*Momordica charantia*) [10-13], alfalfa (*Medicago sativa*) [14], elmberry (*Filipendula ulmaria*) [15], common beans (*Phaseolus vulgaris*) [16], dioecious nettle (*Urtica dioica*) [17] and some other plants.

There is a widespread opinion among researchers that the pharmacological effect of these medicinal plants is due to the presence of chemicals in them that can act directly on the pathological chain of the disease, as well as indirectly, facilitating the course of the disease, preventing the development of complications, helping the body to adapt faster. In other words, the mechanism of action of phytotherapy in diabetes mellitus is considered from the standpoint of traditional pharmacology without taking into account the role of the dosage form. Namely, the mechanism of action of herbal mixtures is being investigated without taking into account the fact that not a dry vegetable mixture is injected into the body of a diabetic patient, but an aqueous extract of vegetable raw materials [18,19]. Nevertheless, the mechanism of action of aqueous extracts of plant raw materials in diabetes mellitus has not been definitively studied.

Diabetes mellitus is an endocrine disease based on relative or absolute insulin insufficiency. According to the data of the International Diabetes Federation (IDF) for 2015, there are 415 million people with diabetes in the world, of which 12.1 million people are in the Russian Federation, and by 2040 the number of diabetic patients is projected to increase to 642 million people [20]. Due to its prevalence, diabetes mellitus is an important health problem, and therefore measures are being taken to control the development of the disease and improve the quality of life of patients, new drugs and treatment methods are being sought. At the early stages of the development of type 2 diabetes mellitus, special attention is paid to phytotherapy, as well as measures for the formation of a healthy lifestyle [21]. Phytotherapy of diabetes mellitus is aimed at reducing blood glucose, as well as preventing the development of concomitant complications of the disease. At the same time, phytopreparations do not contain insulin.

So, phytotherapy of type 2 diabetes mellitus pursues the goal of preventing the disease. Currently, phytopreparations remain in demand, fashionable and safe means of treating patients with diabetes mellitus. However, the mechanism of action of the medicinal plants used and the aqueous extracts obtained from them has not been fully studied.

2. THE ESSENCE OF THE PROBLEM

The essence of phytotherapy of diabetes mellitus is that patients do not take dry vegetable raw materials inside, but drink 250 mL/d of tea, infusion and/or decoction obtained using traditional technology with the help of hot water and raw materials [22]. At the same time, most researchers and doctors are of the opinion that the hypoglycemic effect is associated with plant raw materials, namely, with some active compounds that may be contained in raw materials [23]. At the same time, the water that forms the basis of tea, infusion or decoction is not taken into account.

In particular, it is reported that experiments on Wistar rats with diabetes mellitus have shown hypolipidemic and antioxidant effects associated with the introduction of extracts of blueberry leaves and bean leaves [24]. However, in this study, the authors did not take into account the influence of water, which was in the extract of vegetable raw materials. Similarly, the role of the

injected water was not taken into account in the experimental study of the hypoglycemic activity of aqueous extraction and individual phenolic compounds of eugenol basil (*Ocimum gratissimum* L.) *in vivo* on a model of streptozocin-induced diabetes. The authors associated the hypoglycemic results obtained with the administration of only aqueous extraction to animals at doses of 300 mg/kg, 240 and 80 mg/kg. Therefore, the authors concluded that among the main phenolic compounds, chicory acid (3 mg/kg) had a significant effect, which reduced the glycemic levels of diabetic mice by 53% 120 minutes after administration [25]. Based on these ideas, the mechanism of action of phenols is further considered. At the same time, it is believed that phenols are capable of forming peptide complexes with target proteins of enzyme systems, cellular receptors [26]. On the basis of which it is concluded that, the hypoglycemic effect of phenolic substances can be mediated by several mechanisms at once [27,28]:

1. Inhibition of the breakdown of complex carbohydrates.

It is believed that carbohydrates, entering the body with food, are broken down to monosaccharides under the action of enzymes. The resulting glucose is immediately absorbed and enters the bloodstream. The key enzymes involved in the breakdown of complex carbohydrates are α -amylase and α -glucosidase. Inhibition of these enzymes leads to a slowdown in the breakdown of complex carbohydrates and, as a consequence, glucose absorption into the blood [29]. The ability of some phenols (luteolin, luteolin-7-glucoside) to inhibit the above-mentioned enzymes is comparable to the action of acarbose, a drug used in clinical practice [30].

2. Inhibition of glucose absorption in the intestine.

This mechanism of action is based on the idea that glucose absorption in the intestine occurs with the help of transport proteins: SGLT1 (sodium-dependent transport protein) at low glucose concentrations and GLUT2 at high glucose concentrations. At the same time, *in vitro* studies have revealed the inhibitory effect of flavonoids and phenolic acids on glucose protein carriers [27,31].

3. Protection of pancreatic β -cells from destruction.

It is shown that prolonged hyperglycemia leads to an increasing dysfunction of β -cells, manifested in a decrease in insulin secretion, a decrease in the expression of genes responsible for insulin production, and, ultimately, a loss of β -cell mass [32]. It is assumed that phenolic compounds, being powerful antioxidants, protect the β -cells of the islets of Langerhans from the destructive action of reactive oxygen species, and also prevent the development of complications of the disease associated with the cardiovascular system and energy processes [31,33].

4. Ensuring the transport of glucose into tissue cells.

The fact is that glucose penetrates into the cells of muscle and adipose tissue with the help of transport proteins GLUT4 and, to a lesser extent, GLUT1, the movement of which is regulated by insulin [34]. In turn, in the experiment it was established the effect of some phenolic substances on increasing glucose transport into muscle and/or adipose tissue cells was established. The effect of these substances is due to their effect on various cellular mechanisms of stimulating the translocation of the GLUT4 protein (mainly through the activation of adenosine monophosphate kinase (AMPK) and/or phosphoinositide-3 kinase) [27,31,34].

5. Regulation of glucose release by the liver.

It is known that glucose entering the body is partially deposited in the liver in the form of glycogen polysaccharide. In case of an increase in the body's need for glucose, the liver supplies it to the blood through the breakdown of glycogen or its synthesis from non-carbohydrate substrates. These processes are regulated by various hormones. So, insulin inhibits the production of glucose by the liver. Accordingly, in diabetes mellitus, lack of insulin leads to increased glucose production by the liver, which further exacerbates hyperglycemia [31]. Phenolic compounds can affect the activity of liver enzymes, thereby affecting the release of glucose by the liver. Thus, by inducing glucokinase, phenols activate the processes of gluconeogenesis, and the induction of AMPK leads to inhibition of gluconeogenesis and reduces the accumulation of lipids in the liver [27,31].

6. Acceleration of glucose excretion from the body.

It is reported that some phenols have a choleric and diuretic effect, which helps to remove glucose from the body and reduce hyperglycemia [35].

It follows from this that researchers explain the mechanism of hypoglycemic action of aqueous extracts of plant raw materials by the presence of phenol in them, without taking into account the role of water contained in infusions, teas and decoctions.

Another group of chemicals that is found in extracts of many plants is the group of polysaccharides. It is reported that polysaccharides have enveloping and expectorant effects, have immunomodulatory properties, and also have an effect on carbohydrate and lipid metabolism, which can be an important component in the treatment of patients with diabetes mellitus [36-39]. It has been shown that polysaccharides isolated from dogwood fruits (*Cornus officinalis* Sieb. et Zucc.), have an insulin-sensitizing effect by increasing insulin secretion and stimulating the proliferation of β -cells in the pancreas, and also increase the glycogen content in the liver and skeletal muscles [40]. The most famous polysaccharide used in the treatment of diabetes mellitus is inulin, a high-molecular polysaccharide based on fructosans. The prospects of using inulin in the treatment of type 2 diabetes mellitus is that it is able to reduce only elevated blood glucose levels without affecting normal glycemia. Its pharmacological effect, according to literature data, is provided by several mechanisms:

- Inulin promotes the formation of islets of Langerhans in the pancreas and therefore increases the formation of insulin [41].
- Inulin increases the fructose content, enhances glycolysis and inhibits gluconeogenesis, which contributes to the normalization of blood glucose levels [42].
- Inulin protects the β -cells of the islets of Langerhans from destruction, which preserves their insulin-forming activity [43].
- Inulin has a choleric effect, which accelerates the excretion of glucose from the body [44].

It is also reported that inulin regulates not only carbohydrate, but also lipid metabolism, which reduces the risk of many complications of

diabetes mellitus [45]. In addition, it has been shown that inulin improves the digestibility of zinc and copper, which have a hypoglycemic effect [46].

Consequently, another explanation of the hypoglycemic effect of aqueous extracts of plant raw materials is reduced to explaining the hypoglycemic role of the polysaccharides contained in them. But at the same time, the hypoglycemic role of water contained in infusions, teas and decoctions is not considered.

A number of researchers additionally pay attention to the fact that extracts of plant raw materials contain trace elements, which, in their opinion, can also have a hypoglycemic effect. It is reported that trace elements such as magnesium, chromium and vanadium are important for the treatment of diabetes mellitus. Chromium and vanadium have been shown to increase the number of insulin receptors and enhance the binding of insulin to them [47]. Vanadium in the experiment facilitates the utilization and metabolism of glucose, stimulates the secretion of insulin and increases the sensitivity of tissues to it [42,47]. The effect of magnesium has not been precisely established, but it is assumed that it stimulates insulin secretion and affects the utilization of glucose by peripheral tissues [48,49].

And finally, a number of researchers are trying to prove the probability of a hypoglycemic effect in some plant extracts due to the presence of some other biologically active substances in them. So, it was reported antidiabetic activity of berberine contained in common barberry (*Berberis vulgaris*) has been reported [50]. Some sugar-lowering activity of halogen-containing berberine (chlorberberine, bromberberine and iodberberine) has been shown. Although the mechanism of their action has not been definitively established [51]. It is reported that vindogentianin isolated from the extract of the leaves of *Catharanthus roseus* (L.) G. Don. has some hypoglycemic effect, which may be due to increased glucose uptake [52]. It has been shown that guanidine alkaloids isolated from plants of the genus *galega* (galegin, peganin, vasicin) contribute to an increase in the number of beta cells and insulin production [53-55]. On the other hand, it is reported that the norpseudotropin alkaloids calistegins contained in *calystegia* are able to competitively inhibit α -glucosidase, which reduces the process of splitting complex carbohydrates [56].

Other researchers believe that the use of aqueous extracts of plants such as *aralia* (*Aralia mandshurica*), *zamaniha* (*Oplapanax elatus*), *eleutherococcus* (*Eleutherococcus senticosus*), sugar beet root crops (*Beta vulgaris*) [57-60], blue cyanosis (*Polemonium caeruleum*), *momordica* (*Momordica balsamina*) [61,62], willow sarcococcus (*Sarcococca saligna* L.) [63] and nightshade fruits (*Solanum anguivi*) [59] have a sugar-lowering effect due to the content of saponins. In this regard, the collections of these plants and the individual compounds contained in them are considered as potential sugar-lowering agents [64-68]. At the same time, these researchers do not take into account the role of water contained in teas, infusions and decoctions, despite the fact that water is the main and common ingredient of all water extracts of various plant raw materials.

3. WATER AS A PHARMACOLOGICAL AGENT

Phytotherapy for type 2 diabetes is done by drinking on an empty stomach 250 ml of fresh water infusions, decoctions and/or teas, which are made just before consumption. For this purpose, combined vegetable raw materials (a mixture of different parts of different plants) and hot drinking water are used. The fact is that phytotherapy should be carried out for many days and weeks, and water extracts from plants during storage can deteriorate and lose their medicinal properties. Therefore, water extracts are prepared daily, and vegetable raw materials are stored in dry form. This plant raw material can be packed in boxes with a total weight intended for multi-day course phytotherapy, or in separate bags containing single doses of dry plant raw materials. In this case, vegetable raw materials can be crushed and/or ground.

Thus, the process of herbal medicine is very similar to the traditional daily ingestion of a cup of ordinary Chinese tea. At the same time, in both cases, the intake of water extract throughout the world is traditionally dosed by the volume of water extract in milliliters. And this is not accidental. Water is really a very important agent. It has been shown that water in natural conditions usually has weak acidic activity, has hypotonic activity, contains dissolved gases and various trace elements [69]. Therefore, water extracts (infusions, decoctions and teas) prepared from dry vegetable raw materials and water certainly contain not only elements extracted from plants, but water. In turn, any

water extract has a certain pH value and the value of osmotic activity. In addition, any volume of water extraction has a well-defined temperature. At the same time, it has been shown that such physicochemical properties of water and aqueous solutions as the value of acid (alkaline) activity, the value of osmotic activity, the value of temperature and the presence of gases dissolved in water are of great importance for their pharmacological activity [70-73]. At the same time, the volume of water is an independent factor of interaction. The fact is that water (and water extracts) with hypotonic activity is quickly absorbed into the blood from the gastrointestinal tract, after which the water in the blood immediately dilutes the plasma. Dilution of plasma with water reduces the concentration of all substances dissolved in it, including glucose, and reduces the osmotic activity of plasma. Therefore, ingestion of 250 ml of water (infusion, decoction or tea) inside, as well as injection of 10 – 250 ml of water under the skin, intramuscularly or into a vein has a hypoosmotic and hypoglycemic effect.

In this regard, we have to revise the results of experimental and clinical studies of phytotherapy in the future in order to clarify the mechanism of action of aqueous extracts of medicinal plants. To do this, we have to clarify, on the one hand, the physico-chemical properties of infusions, decoctions and teas, on the other hand, the dose of consumed water and the effect of certain volumes of water with a certain osmotic and acidic (or alkaline) activity and other physico-chemical properties on osmotic pressure, alkaline plasma activity of a patient with diabetes mellitus (i.e. not only on the blood sugar level) and on the "washing" of the body.

4. CONCLUSION

Thus, at present, the technology of using mixtures of herbal raw materials for therapeutic purposes in diabetes mellitus is carried out with the use of drinking water. However, the mechanism of action of phytopreparations is traditionally analyzed without taking into account the quality and quantity of water used to prepare infusions, decoctions and teas from medicinal plants. In this connection it is proposed to analyze the therapeutic properties attributed to various phytopreparations, taking into account the volumes of infusions, decoctions and teas, their osmotic, acid (alkaline) activity and temperature. It is shown that ingestion of such water extracts dilutes blood plasma and

promotes "flushing" of the body. Therefore, traditional phytotherapy, based on oral intake of 250 ml of water extracts 2 - 4 times a day, is accompanied by hypoglycemia and a decrease in the concentration of all other blood plasma ingredients. At the same time, some glucose is removed with water from the body during urination and perspiration. Nevertheless, new and more comprehensive research is needed to give a definitive answer to the role of herbal teas and infusions in phytotherapy of diabetes mellitus.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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