

Evaluation of prognostic allergological risks of the inclusion of plant extracts in the composition of drugs and specialized food products for patients
type 2 diabetes

M.A. Kiseleva, T.L. Kiseleva, A.A. Kochetkova, V.A. Tutelyan
(Federal Research Center for Nutrition, Biotechnology and Food Safety, St.
Moscow)

Prognostic allergological risk evaluation of plant extracts in herbal medicines and specialized food products for patients with type 2 diabetes

MA Kiseleva, TL Kiseleva, AA Kochetkova, VA Tutelyan
Federal Research Center of Nutrition and Biotechnology (Moscow, Russia)

SUMMARY

Taking into account international recommendations on the predictive assessment of the safety of herbal preparations and specialized food products, a preliminary informational assessment of potential allergological risks of using 13 medicinal plants - promising sources of drugs and phytonutrients for specialized food products for patients with diabetes mellitus was carried out. Of the 13 most commonly used domestic medicinal plants in traditional recipe guides for the treatment of diabetes mellitus, the most prognostically safest sources of phytonutrients (in terms of their allergological and toxicological risks) are blueberry leaves and shoots.

Key words: specialized food products, herbal medicines drugs, diabetes mellitus, blueberry, allergological risks, predictive safety assessment.

RESUME

In accordance with international recommendations for prognostic safety assessment, we analyzed the potential allergic risks of 13 plants which are considered as the most prospective components of herbal products and specialized food products for patients with type 2 diabetes. Among the 13 commonly used medicinal plants for diabetes treatment leaves and shoots of bilberry can be considered as the most harmless sources of phytonutrients from the standpoint of their low allergological and toxicological risks.

keywords:specialized food products, herbal medicines, diabetes, bilberry, potential allergological risk, predictive safety evaluation.

Diabetes mellitus (DM) is one of the most widespread socially significant diseases characterized by the development of severe disabling complications [5, 6]. Despite the undoubted successes of modern endocrinology and diabetology, the high quality of drugs used in the treatment of diabetes, the development of new technologies for its treatment, the level of disability and mortality of patients is not significantly reduced, and the number of cases not only does not decrease, but is steadily increasing, and in all age groups and social strata of the population [5].

Medicinal plants (MP) are traditionally used to treat DM in almost all countries and traditional medical systems of the world [9, 17, 20, 54, 88] and serve as raw materials for the production of herbal preparations. For today

day also proved the feasibility of their use as sources of micronutrients for specialized foods (SPF) with an optimized composition

[15–17, 21, 22]. At the same time, there is a significant amount of information about undesirable side reactions when using drugs [3, 24, 26-28, 30, 37, 44, 78, 97], and most often they cause allergic reactions (about 50 types of drugs) [3, 27].

According to modern concepts, allergists, clinical immunologists, endocrinologists and other specialists should be well informed themselves and inform patients about possible side effects and hypersensitivity reactions when using medicinal and food plants [29], however, thematic scientific publications on allergological and other risks of using medicinal plants in diabetes mellitus, in the available literature, we not found.

In accordance with the plan of scientific research under the grant of the Russian Science Foundation "Specialized food products with a modified carbohydrate profile for personalized diet therapy for type 2 diabetes" (14-36-00041), we previously analyzed 550 traditional herbal antidiabetic recipes from 66 recipe guides in Russia, Belarus and Ukraine and identified the most common herbal ingredients in their collections, which can presumably serve as promising sources of phytonutrients for specialized food products with an optimized composition for patients with diabetes mellitus [18–20]. As a result of the study, we identified 13 most commonly used plants,

Taking into account the harmonization of the requirements for the safety of medicinal plant materials in force in the Russian Federation with the requirements adopted in the EU and the USA, before conducting experimental (pharmacological) studies of plant extracts of identified 13 plant species, we considered it appropriate to predictively evaluate possible allergological and other risks of their use as sources of herbal preparations and phytonutrients in the development of specialized food products for patients with diabetes mellitus.

The purpose of this study is to identify, analyze and summarize reliable information on possible adverse reactions to herbal extracts and biologically active substances of medicinal plants, which are promising sources of drugs and micronutrients for specialized food products for patients with diabetes.

The focus of this work was only established allergic and other undesirable side reactions when using medicinal plant materials and biologically active substances from it, but not questions of toxicity due to exogenous and endogenous factors.

Materials and methods

The objects of the study were regulatory documents and other reliable bibliographic sources: scientific periodicals (PubMed), scientific and official publications, and international databases containing information about allergens and side effects of medicinal plants and products based on them. When assessing allergological risks, we took as a basis information from the electronic database of the official website of the Subcommittee on Allergen Nomenclature of the International Union of Immunological Societies of WHO (WHO/IUIS SubCommittee on Allergen Nomenclature) [24], and also used the official materials of EAACI (European Academy of Allergy and Clinical Immunology) [74, 75, 86, 102], FDA [37], American Herbal Products Association (AHPA) [26]. The following research methods were used: descriptive, quantitative, informational, historical, analytical,

The relevance of assessing allergological and other risks of drug use
plants and products based on them
The problem of food and drug allergies remains one of the most

widespread in almost all countries of the world and relevant both for patients of various age groups and for society as a whole [39, 50, 51, 74, 75].

The effectiveness of clinical measures to prevent food allergies, according to experts, is still insufficient and requires special study [51]. Competent evidence-based interaction with specialists prescribing and dispensing medicines (doctors, paramedical staff, pharmacy workers), as well as with persons dispensing food and helping with the proper choice of products (with employees of hospitals, kindergartens, schools, restaurants, etc.), reduces the risk of serious (sometimes fatal) reactions to food and drugs, including those of plant origin [51, 73–75].

Informing doctors and patients at risk of developing allergic reactions and/or intolerance is an extremely important aspect of preventing the occurrence of critical situations for both patients and people who consider themselves healthy people [74, 75]. In recent years, experts have also paid increased attention to awareness in this area among government officials, believing that this can improve decision-making on issues of legislation at the local and state levels aimed at improving the safety of patients and food consumers [74].

A special place in the process of improving the safety of using natural medicinal plant raw materials should be given to the development of herbal medicines and specialized food products based on food and medicinal plants that have minimal allergological and other risks of using medical, pharmaceutical and food products in these categories.

Numerous prospective randomized controlled trials on the safety of the use of medicinal plants, medicinal herbal raw materials and products from it have made it possible to accumulate a certain amount of information about possible adverse reactions from the standpoint of evidence-based medicine [26, 44, 97]. However, up to 70% of patients using herbal medicines, herbal medicines and herbal food products are not informed about the side effects of herbal ingredients and their possible interactions with synthetic drugs. Therefore, they cannot assess the potential danger from their use [4]. The doctor also does not always have the opportunity to take into account all the potential risks from the use of herbal medicines, biologically active additives (BAA) to food and other plant-based products [2, 3]. Given the expediency of using medicinal plants as promising sources of phytonutrients for specialized food products with an optimized composition [9, 17–19, 21, 23], this problem becomes extremely relevant for both dietology and the food industry.

Abroad, a significant amount of information about adverse reactions in the use of medicinal plants in clinical practice and as part of dietary supplements has already been summarized in the form of several monographs [3, 28, 30] and in the form of specialized databases that are constantly updated [37, 44, 53, 78, 79]. According to experts, among all known adverse reactions, non-poisonous food and medicinal plants (about 50 types of medicinal products) most often cause allergic reactions [3, 4, 27].

Scientifically substantiated information about medicinal plants, groups of biologically active substances (BAS), individual BAS or plant extracts that cause allergic reactions or increase the sensitivity of patients to other chemical compounds continues to accumulate actively. In particular, it has been found that patients sensitive to salicylates may develop allergic reactions to white willow preparations [94]. Allergic reactions to coumarins, anthocyanins [3] and to metabolic products of burdock root lignans have been recorded [28]. It has been shown that a number of terpene derivatives (including those from mint oil [28, 35, 103]) significantly increase the sensitivity of patients to various chemical compounds [87].

However, the newly emerging works are still scattered, and their results are often

contradict the previously published data [3], which, in turn, need to be analyzed, generalized, and systematized. The National Guidelines for Allergology and Immunology [1] contain an extremely limited amount of information related to the risks of using medicinal plants and products based on them.

The assessment of allergological risks in the food industry in developed countries is becoming an indispensable element in the development and production of food products [40, 73, 74]. It is obvious that the assessment of allergological and other risks of phytotherapy should also become one of the routine stages of evidence-based treatment and prevention using medicinal plants in all age groups of the population, especially in children, including the development of specialized food products. And the creation of databases on the allergological risks of the use of medicinal plants, herbal medicines and specialized food products based on them is today an urgent task of medical and pharmaceutical sciences.

Assessment of potential allergological and other risks of drug use plants for the treatment of diabetes

As a result of the analysis of 550 traditional herbal antidiabetic recipes from 66 recipe guides in Russia, Belarus and Ukraine, we identified 13 most commonly used plants, which are included in more than half of the studied traditional guides as part of antidiabetic recipes [20]. The results of the prognostic informational assessment of potential allergological risks of using these 13 plant species as promising sources of phytonutrients in the development of specialized food products for patients with diabetes are summarized in Table. one.

A comparative analysis of our own research results with the WHO/IUIS Allergen Nomenclature made it possible to establish that from Of the 13 studied plant species, today only 2 species are included in this database [24]: common bean - *Phaseolus nanus* L. and garden strawberry (strawberry) - *Fragaria ananassa* (Strawberry) (Table 1). No information was found in the Nomenclature about 11 plants out of 13 studied.

Comparative analysis with data on food allergens. Of the studied 13 plant species of 7 species are included in the National Guidelines for Allergology and Immunology [1]. Of these, 4 species are classified as food allergens - oats, common chicory, peppermint, common beans (white, red, green beans and asparagus (curly) [1].

There are data on the development of anaphylaxis and anaphylactic shock [28, 93] after oral consumption of burdock root decoction (Table 1). In an in vitro experiment, arctiin lignan undergoes cleavage (at the glycosidic bond) to form arctigenin aglycone [28, 80]. Its demethylation in the intestine of rats at the 3''-position creates a secondary metabolite 2-(3'',4''-dihydroxybenzyl)-3-(3',4'-dimethyl-butylolactone), which may be the cause of anaphylactic reactions. [28].

Table 1

Possible allergic and other risks when using the most popular herbs from traditional antidiabetic formulations (in descending order of frequency of use plants in 66 recipe directories in Russia, Belarus and Ukraine)

№	Русское и латинское название растения и семейства	Возможные аллергические реакции при применении в составе готовых препаратов и пищевых продуктов	Примечание: предостережения и противопоказания к применению
1	2	3	4
1	Черника обыкновенная <i>Vaccinium myrtillus</i> L. Сем. Брусничные – Vacciniaceae	В очень больших дозах препараты плодов могут вызывать кожные проявления аллергии [3].	Препараты плодов малотоксичны, но в очень больших дозах могут вызывать функциональные нарушения ЖКТ [3].
2	Фасоль обыкновенная <i>Phaseolus nanus</i> L. <i>Phaseolus vulgaris</i> (L.) Savi var. nana Ach. Сем. Бобовые – Fabaceae	Фасоль: белая, красная, стручковая и спаржевая (вьющаяся) – относится к пищевым аллергенам [1]. Имеется риск развития перекрестных аллергических реакций у пациентов при наличии сенсибилизации к сое, арахису и другим бобовым [1]. Выявленные алергокомпоненты: Pha v 3. Биохимическое название: non-specific lipid transfer protein type 1, молекулярная масса 8,8–9,0 кДа [24].	Помимо индивидуальной непереносимости, других противопоказаний к применению створок фасоли в доступных библиографических источниках не обнаружено.
3	Крапива двудомная <i>Urtica dioica</i> L. Крапивиные – Urticaceae	Имеются сообщения о кожных проявлениях аллергии [99, 103], в том числе уртикарной сыпи [3]. Корни, листья и трава противопоказаны при аллергических реакциях на растения семейства Urticaceae (Крапивиные) [103].	В связи с возможным влиянием на метаболизм андрогенов и эстрогенов, применение корней крапивы во время беременности и лактации, а также для лечения детей в возрасте до 12 лет противопоказано [3, 7, 8, 103]. Имеются сообщения о побочных эффектах со стороны желудочно-кишечного тракта: диарея, боли в животе и тошнота [99, 100, 103]. С осторожностью при склонности к гиперкоагуляции [8], заболеваниях ЖКТ [3].
4	Одуванчик лекарственный <i>Taraxacum officinale</i> Wigg.s.l. Сем. Астровые – Asteraceae	Имеются сообщения об аллергических реакциях [3], включая анафилаксию и контактный дерматит [33, 34, 61, 64]. Потенциальными аллергенами могут являться в т.ч. горечи терпеноидной структуры [7]. Подтверждены аллергологические риски у пациентов при наличии аллергии на пыльцу полыни и амброзии [1]. Отмечена перекрестная чувствительность у отдельных лиц с аллергией на пыльцу других растений семейства Астровых (Сложноцветных) [43, 103].	Препараты малотоксичны [3, 103]. Противопоказаны при билиарной обструкции, непроходимости кишечника, остром холецистите [103], острых заболеваниях желудка и 12-перстной кишки [8]. Могут вызвать повышение кислотности желудочного сока (горечи) [30, 103]. Применения следует избегать при дискинезии желчевыводящих путей и нарушениях моторики кишечника [7]. Возможно уменьшение всасывания ципрофлоксацина со снижением его концентрации в плазме [3].
5	Шиповник майский (коричный) и др. виды – <i>Rosa majalis</i> Herrm. – (<i>Rosa cinnamomea</i> L.) Сем. Розоцветные – Rosaceae	Прием в дозах, превышающих терапевтические, или длительное применение провоцируют аллергические реакции. Риск их появления возрастает на фоне лечения антибактериальными препаратами или препаратами сульфаниламидного ряда [7]. Отмечена перекрестная чувствительность у лиц с аллергией на другие растения семейства Розоцветных (яблоки) [1]. Описаны аллергические реакции при приеме в составе Сборов витаминных № 1 и № 2, а также сиропа плодов шиповника [7].	Плоды (настой) противопоказаны при гиперацидных гастритах, тромбозах, эндокардитах, недостаточности кровообращения (в высоких дозах способствуют появлению отеков) [8]; отвар корней и спиртовая настойка плодов – при гипертонической болезни [7, 8]. Рекомендуемая профилактическая доза вит. С – 45–60 (до 70) мг в сутки [7]. В чрезвычайно высоких дозировках витамин С обладает тератогенным действием, в завышенных – способствует образованию конкрементов и повышает риск тромбозов, кровотечений в акушерско-гинекологической практике [7]. Настой плодов и препараты аскорбиновой кислоты не назначают в высоких дозировках при гиперацидных гастритах, тромбозах, эндокардитах, недостаточности кровообращения. Длительный прием противопоказан при гипертонической болезни [8], может спровоцировать рецидивы флебитов [7].
6	Земляника лесная – <i>Fragaria vesca</i> L. Сем. Розоцветные – Rosaceae	Описаны аллергические реакции (особенно у детей до 3 лет) при приеме земляники ананасной и лесной, проявляющиеся как правило рецидивирующей крапивницей и кожным зудом [8]. Ангиоотек может быть спровоцирован даже запахом земляники [7]. Земляника и клубника часто вызывают псевдоаллергические (неймунологические) реакции за счет гистаминолибераторов, гистамина и ароматических веществ [1]. Выявленные алергокомпоненты: Fra a 1. Биохимическое название: Pathogenesis-related protein PR-10, Bet v 1 family member, молекулярная масса 18 кДа. Fra a 3. Биохимическое название: Non-specific lipid transfer protein type 1 (nsLTP1), молекулярная масса 9 кДа. Fra a 4. Биохимическое название: Profilin, молекулярная масса 13 кДа [24].	Плоды противопоказаны при гиперацидных состояниях, печеночных и почечных коликах, аппендиците [7]. В больших дозах не рекомендуется беременным и детям. С осторожностью – при повышенной кислотности желудочного сока, рецидивирующих печеночных и почечных коликах [8]. Рекомендуемая доза бета-каротина 30–300 мг для взрослых и 15–150 мг для детей [7]. По некоторым данным, земляника и препараты из нее вообще не рекомендуются беременным [7].
7	Лопух большой – <i>Arctium lappa</i> L. Сем. Астровые – Asteraceae	Возможно развитие системных аллергических реакций (анафилактический шок, ангиоотек) и реакций со стороны органов дыхания (удушие) на фоне перорального применения извлечений из корня лопуха [28]. Отмечена перекрестная чувствительность у отдельных лиц с аллергией на пыльцу других растений семейства Астровых (Сложноцветных) [43].	Плоды противопоказаны при диарее [8].

№	Русское и латинское название растения и семейства	Возможные аллергические реакции при применении в составе готовых препаратов и пищевых продуктов	Примечание: предостережения и противопоказания к применению
1	2	3	4
8	Мята перечная – <i>Mentha piperita</i> L. Сем. Яснотковые – <i>Lamiaceae</i>	Трава относится к пищевым аллергенам, возможны перекрестные реакции с шалфеем [1]. Описаны системные аллергические реакции при приеме мятного масла внутрь: анафилактический шок, ангионевротический отек, а также реакции со стороны органов дыхания (бронхоспазм, удушье) [7, 28, 32, 68]. Аллергические реакции на пероральный прием мятного масла (в том числе в составе сложных смесей и продуктов) могут проявляться также в виде высыпаний на коже, в т.ч. уртикарных, кожного зуда, головной боли, головокружений, диспепсии, дизурии [7, 28, 32, 68]. Мятное масло, как и другие эфирные масла, вызывают аллергические реакции не только при пероральном приеме, но и при контакте с кожей и слизистыми: контактные дерматиты, рецидивирующие афтозные стоматиты [7, 28, 41, 47, 71, 82, 103]. Описана гиперчувствительность к мятному маслу и ментолу при наружном применении [35, 45, 92, 103], а также повышенная индивидуальная чувствительность. Помимо ментола, сенсibilizаторами могут служить другие терпеновые производные мяты, например, -пинен, дипентен, фелландрен и др. [28, 35].	Противопоказания для приема препаратов листьев и травы: беременность, детский возраст до 5 лет [7, 8, 30, 103]. Без медицинского наблюдения не следует применять пациентам с желчнокаменной болезнью и гастритом, беременным женщинам [30, 103]. Мятное масло противопоказано при воспалительных заболеваниях ЖКТ или желчного пузыря и при нарушениях функции печени [30, 103]. При передозировке любых препаратов мяты возможно появление реакций со стороны пищеварительной системы (тошнота), органов дыхания (бронхоспазм, удушье) и сердечно-сосудистой системы (кардиалгия, гипотония, брадикардия) и центральной нервной систем (судороги, тремор, атаксия) [7, 8, 28, 32, 68]. Побочные эффекты: изжога, усиление менструальных кровотечений [3]. Все лекарственные формы (в т.ч. эфирное масло) в больших дозировках угнетают ЦНС [8]. В стоматологии чрезмерное длительное использование продукции на основе мяты ассоциировано со стоматитами и гипертрофией сосочков на языке [28, 91].
9	Цикорий обыкновенный - <i>Cichonum intubus</i> L. Сем. Астровые – <i>Asteraceae</i>	Относится к пищевым аллергенам [1]. Отмечена перекрестная чувствительность у лиц с аллергией на пыльцу других растений семейства Астровых (Сложноцветных) [43].	Противопоказаний к применению в доступной литературе не выявлено.
10	Зверобой продырявленный (обыкновенный) – <i>Hypericum perforatum</i> L., Зверобой пятнистый (четырёхгранный) – <i>Hypericum maculatum</i> Crantz (H. quadrangulum L.) Сем. Зверобойные – <i>Hypericaceae</i>	Имеются сообщения о наличии значительного числа побочных эффектов и реакций гиперчувствительности при применении зверобоя [29]. Аллергические реакции наиболее часто проявляются в виде кожного зуда [7]. Любые извлечения из травы противопоказаны в случаях известной аллергии к растениям семейства <i>Clusiaceae</i> (Клюзиевые) [103]. Причиной появления выраженных аллергических реакций может служить одновременный прием препаратов зверобоя с антибактериальными средствами [7]. За счет ускорения биотрансформации антигистаминных лекарственных средств на фоне препаратов зверобоя возможно ослабление их противоаллергического эффекта [3].	Противопоказания: беременность, лактация [3]. На фоне приема препаратов следует избегать методов лечения с использованием ультрафиолета или длительного пребывания под прямыми солнечными лучами из-за возможной фотосенсибилизации [30, 103]. Также вследствие фотосенсибилизирующей активности конденсированных производных антрацена при приеме в летнее время могут возникать ожоги и кожные эритемы [8]. Длительный прием и передозировка препаратов могут привести к развитию артериальной гипертензии (сосудосуживающее действие), обострению хронических заболеваний ЖКТ, возникновению стойких запоров (дубильные вещества) и нарушению биоценоза кишечника (выраженная бактерицидная активность), особенно у лиц пожилого возраста. С осторожностью – при желчнокаменной болезни, хронических болезнях почек [8].
11	Хвощ полевой - <i>Equisetum arvense</i> L. Сем. Хвощовые – <i>Equisetaceae</i>	Возможно появление дерматитов при применении препаратов хвоща на фоне диеты с высоким содержанием холестерина [52, 103]. Препараты не используют вновь после появления реакции гиперчувствительности к ним [103].	Препараты противопоказаны при беременности (утеротоническое действие) [12, 103], острых и хронических заболеваниях почек в период обострения (раздражают почечную паренхиму) [8, 10, 11, 103], отеках при заболеваниях сердца и почек [3]. По другим данным (открытое неконтролируемое клиническое исследование) [14, 103], напротив, позитивный эффект (усиление диуреза при приеме сока из травы в дозе 1 ст. ложка 3 раза в день) был получен у пациентов с сердечной недостаточностью и отеками. В том же исследовании использовали настой (15 г сырья в 180 мл воды) в дозе 1 ст. л. через каждые 2 ч при водянке; диурез усилился более чем у 50 % пациентов [14, 103]. Однако в любом случае пациентам с отеками, вызванными сердечной и почечной недостаточностью, не рекомендуется ирригационная терапия [14, 103]. Препараты не применяют без наблюдения врача более 6 недель (могут вызвать симптомы диспепсии) [46, 103]. Не рекомендуется прием больших количеств травы и препаратов хвоща на фоне диеты с высоким содержанием холестерина [63, 103]. Свежую и высушенную траву и порошки из нее не следует использовать кормящим матерям и в педиатрии [103] из-за содержания неорганических кремниевых компонентов и алкалоидов [38, 103]. Без консультации врача не используют для добавления в ванну даже при значительных поражениях кожи, а также острых поражениях кожи неизвестной этиологии, серьезных лихорадочных и инфекционных заболеваниях, сердечной недостаточности и гипертензии [46, 103]. Особая осторожность необходима при любых заболеваниях, связанных с серьезным нарушением деятельности и воспалениями почек (нефрит, нефроз) [10, 11, 103].

№	Русское и латинское название растения и семейства	Возможные аллергические реакции при применении в составе готовых препаратов и пищевых продуктов	Примечание: предостережения и противопоказания к применению
1	2	3	4
12	Овес посевной – <i>Avena sativa</i> L. Сем. Злаковые – Poaceae (Gramineae)	Относится к пищевым аллергенам [1]. Имеется аллергологический риск у лиц с аллергическими реакциями на злаки, пыльцу злаковых трав, а также на растения семейства Крестоцветных (Капустных) и Лилейных (перекрестные аллергические реакции) [1]. Возможны негативные реакции у пациентов с сенсибилизацией к глютену [3]. Витамины В12 усиливает аллергические реакции, вызываемые витамином В1 [7].	Противопоказания: непереносимость глютена [3]. Настойка из травы противопоказана при острой сердечной и почечной недостаточности [8].
13	Галега (козлятник лекарственный) – <i>Galega officinalis</i> L. Сем. Бобовые – Fabaceae	В доступных библиографических источниках данных не выявлено.	Показано гипотензивное и нейротоксическое действие гуанидинового алкалоида галегина [56].

A significant number of side effects and hypersensitivity reactions have also been described when using St.

Risk analysis of cross-allergic reactions. In the National Guide to Allergology and immunology cross-allergic reactions are described for 5 out of 13 studied species (sowing oats, peppermint, wild rose (various species), medicinal dandelion, common beans) [1].

Our analysis of the potential risks of cross-allergic reactions made it possible to establish that of the 13 studied species of domestic medicinal plants (promising sources of phytonutrients for specialized food products for patients with diabetes mellitus) included in Table. 1, the Asteraceae (Composite) family includes 3 plants, the Legume and Rosaceae families - 2 plants each, the Cowberry, St. John's wort, Cereal, Nettle, Horsetail and Lamiaceae families - 1 plant each.

Of these families, the most unfavorable allergological prognosis is for representatives of the Astrov family. Official WHO documents contain indications of cross-allergic reactions between inhalation and food allergens of various representatives of this family [43, 103]. In the present study, 3 species of plants belong to it: medicinal dandelion - *Taraxacum officinale* Wigg.sl, great burdock - *Arctium lappa* L., common chicory - *Cichonum intubus* L.

Since popular food plants of this family (sunflower, artichoke, Jerusalem artichoke, lettuce, etc.) are usually included in the diet therapy of diabetes mellitus, the possibility of cross-allergic reactions in patients should be taken into account when creating specialized food products. Particular care should be taken when using phytotherapy in patients with diabetes mellitus using drugs from very popular representatives of this family: chamomile and tongueless, yarrow, arnica, succession, milk thistle, wormwood, tansy, cornflower, coltsfoot, calendula, cudweed, elecampane, echinacea, immortelle and many others. The use of food and medicinal products based on the three plants studied in this work (dandelion,

One of the potentially significant plant allergens included in the WHO/IUIS Nomenclature [24] is the common bean (legume family) – all its subspecies, varieties and forms. As with other members of the legume family, when using beans, there is a high risk of developing cross-allergic reactions in individuals sensitized to soy, peanuts and other legumes [1]. Therefore, despite the high frequency of the traditional use of bean wings in antidiabetic formulations [20], the prospects for the widespread use of its herbal extracts in the composition of specialized food products, apparently, will be

low. The use of individual biologically active substances of hypoglycemic action, isolated from bean leaves, will require special studies. The legume family also includes the alkaloid-bearing plant *Galega officinalis*, or goat's rue, which, among other things, has a neurotoxic effect (Table 1).

Stinging nettle occupies the third line in the list of the most popular ingredients of traditional anti-diabetic recipes. The prognostic allergological risks of nettle use are significantly less significant compared to members of the Asteraceae and Legume families, since cross-allergic reactions to nettle roots, leaves or herb are possible only in the presence of an allergy to other plants of the Urticaceae (Nettle) family [103]. Only 3 representatives of this family belong to the number of plants used in official and traditional domestic medical practice: deaf nettle (Lamb nettle), stinging nettle and dioica nettle itself. Close to the nettle family is the elm or elm family (Ulmaceae), whose representatives have neither nutritional nor medicinal value - smooth elm (*Ulmus laevis*), rough elm,

The studied representatives of the Rosaceae family (rose hips, strawberries) can cause cross-allergic reactions in individuals allergic to other plants of the Rosaceae family (for example, apples, peaches) [1]. Representatives of the Rosaceae family are widely used not only as food plants, but also as sources of medicinal plant materials used, among other things, in the treatment of diabetes mellitus (flowers and fruits of hawthorn, flowers of meadowsweet, rhizomes and roots of burnet, rhizomes of cinquefoil and cinquefoil, rowan fruits, etc.)

St. John's wort closes the top ten of the most popular medicinal plants of traditional antidiabetic formulations (in some formulations - St. John's wort tetrahedral). However, according to the WHO, any extract from St. John's wort is contraindicated in the presence of allergic reactions to plants of the Clusiaceae family (syn.: Comedy) [103], close to St. John's wort, with which it is often combined. Recently, some tropical representatives of this family have become more often eaten by the inhabitants of our country due to the expansion of tourist geography (for example, mangosteen and Antillean apricot).

A high risk of developing cross-allergic reactions exists for plants of the Cereal family, in particular, oats (Table 1), in case of sensitization to other cereals (rice, wheat, rye, etc.) or pollen of cereal grasses, as well as to plants of the families Cruciferous (Cabbage) and Lily. Patients with gluten intolerance may develop negative reactions when taking drugs or eating oat-based foods [3].

Analysis of toxicological risks and risks of adverse reactions. Analysis of modern specialized literature on the issues of toxicity, side effects and contraindications to the use of the most commonly used medicinal plants in traditional antidiabetic formulations, as well as biologically active substances and extracts from them, made it possible to establish the following.

Common blueberry (*Vaccinium myrtillus* L.). Toxicity and side effects of the leaves, shoots and fruits are not established and not described, there are no restrictions on the use. Abuse of fruits can worsen the condition of patients with intestinal motility disorders and biliary dyskinesia of the hypokinetic type [8]. In the experiment, blueberry preparations inhibit the polypeptide transporting organic anions B (OATP-B or SLCO2B1), which can cause an increase in the concentration of LS-substrates of OATP-B (plasma repaglinide) [3].

Anthocyanin derivatives of blueberries inhibit platelet aggregation in animals and humans. In animals, when administered orally at a dose of 5–400 mg/kg, anthocyanides (anthocyanosides) cause bleeding, the severity of which increases with increasing dose [3, 31, 85]. In healthy volunteers, anthocyanins (Myrtocyan) at a dose of 480 mg inhibit aggregation

platelets for a long time [70]. Other types of side effects, contraindications for use and possible allergological risks when using blueberries as part of finished drugs and food products are presented in Table. 1 (column 4).

Common bean (*Phaseolus nanus* L. *Phaseolus vulgaris* (L.) Savi var. *nana* Ach.). Maybe provoke non-immunological reactions due to aflatoxins in seeds (beans). Seeds are contraindicated in gastric ulcer and duodenal ulcer in the acute stage; digested for a long time, increase the formation of gases in the intestines. Excessive consumption of food leads to flatulence, sleep disturbances. In some varieties (bp with bright flowers), the raw seeds are slightly poisonous [8]. In addition to individual intolerance, no other contraindications to the use of bean leaves were found in the available bibliographic sources.

Stinging nettle (*Urtica dioica* L.). Interaction with other drugs not described by means [Bulaev, 2013]. The use of leaves should be strictly dosed with a tendency to hypercoagulability, and long-term use in high doses contributes to the progression of thrombophlebitis and arterial hypertension [7]. According to some reports, atherosclerosis is a limitation to long-term use in high doses [7, 8].

It is not used as a hemostatic agent for bleeding associated with cysts and polyps of the endometrium, benign tumors of the uterus and its appendages [7, 8]. Side effects: irritation of the gastric mucosa, skin rashes, peripheral edema, oliguria [3]. There are data on registered adverse reactions for coumarins and ascorbic acid [3, 27, 59]. Other types of side effects of nettle, contraindications for use and possible risks when used as part of finished drugs and food products are presented in Table. 1 (column 4).

Dandelion medicinal (*Taraxacum officinale* Wigg.sl). Drugs enhance the effect diuretics, reduce the absorption of ciprofloxacin, which is accompanied by a decrease in its plasma concentration [3]. In particular, a decrease in the maximum concentration of ciprofloxacin was observed in rats that simultaneously received orally (2.0 g/kg body weight) an aqueous extract of the whole plant and (20.0 mg/kg body weight) ciprofloxacin [103, 105].

The drugs have low toxicity [3], but their long-term use leads to an increase in blood clotting [7]. Like other sources of bitterness, dandelion can stimulate secretion and increase the acidity of gastric juice, provoke pain in the epigastric region, increase intestinal peristalsis [7, 30, 103], therefore preparations from it are not prescribed for acute and during exacerbation of chronic gastroduodenitis [8]. There are data on registered adverse reactions for coumarins [3, 27, 59]. Other types of side effects of dandelion, contraindications for use and possible risks when used as part of finished drugs and food products are presented in Table. 1 (column 4).

Rosehip May (cinnamon) and other species (*Rosa majalis* Herrn., *Rosa cinnamomea* L.). At long-term use of rosehip preparations in doses higher than therapeutic, there is a risk of developing hepatitis, hypocoagulation and bleeding [7].

A decoction of the fruit can cause edema in patients with heart disease. Long-term use in hypertension may prevent a decrease in blood pressure (the "blocking" effect), even when taking antihypertensive drugs [7]. In the clinic, after three weeks of admission, patients noted an increase in the concentration of potassium and sodium ions in the blood serum at the same time. After 6 weeks, plasma glucose concentration significantly increased and blood clotting time decreased, itching, skin rashes, and weakness appeared [7].

A decoction of the fruit (due to the high content of organic acids) damages the enamel of the teeth, and the syrup can cause flatulence [7].

Like a decoction, fruit infusion and ascorbic acid preparations are not prescribed in high dosages for hyperacid gastritis, thrombophlebitis, endocarditis, and circulatory failure. Long-term use is contraindicated in hypertension [8].

Ascorbic acid and products containing it can weaken the effect of certain drugs, such as combined oral contraceptives, and reduce the absorption of vitamin B12; increase iron absorption, but bind zinc and copper ions in the body [7]. The intake of antioxidants (vit. C, E) in high doses may be associated with an increased risk of premature rupture of the membranes in pregnant women [13, 96]. In the presence of chronic kidney disease, excessive intake of vitamin C can increase crystalluria and contribute to the formation of calculi [7]. In extremely high dosages, vitamin C has a teratogenic effect, in excessive doses it promotes the formation of stones and increases the risk of thrombophlebitis, bleeding; the recommended prophylactic dose is 45–60 (up to 70) mg per day [7]. Beta-carotene in high doses is embryotoxic and contraindicated in pregnant women; the recommended dose is 30–300 mg for adults and 15–150 mg for children [7].

Other warnings and contraindications for the use of rose hips are presented in Table. 1 (column 4).

Wild strawberry (*Fragaria vesca* L.). When taking berries and preparations from them on an empty stomach may cause nausea, abdominal pain [7].

Terpene derivatives can increase the sensitivity of patients to various chemical compounds [87]. Beta-carotene in high doses is embryotoxic and contraindicated in pregnant women; the recommended dose is 30–300 mg for adults and 15–150 mg for children [7]. Other types of side effects of strawberries, contraindications for use and possible risks when used as part of finished drugs and food products are presented in Table. 1 (column 4).

Burdock (*Arctium lappa* L.). Cases of mild poisoning (weakness, dizziness, dry mouth, blurred vision, mydriasis, urinary retention, confusion) after drinking a decoction of burdock root [28, 89]. The fruits are contraindicated in diarrhea [8]. Topical application of the root as a plaster or dressing may cause contact dermatitis [28, 90].

Peppermint (*Mentha piperita* L.). In the experiment, peppermint preparations inhibit CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP3A4, which can cause an increase in the concentration of drug substrates of these cytochrome P450 isoenzymes [3, 28]. In high doses (significantly higher than therapeutic), preparations from the leaves depress the central nervous system, but in some cases cause insomnia. In case of overdose for a long time, the appearance of symptoms of urinary incontinence has been described [7].

Terpene derivatives can increase the sensitivity of patients to various chemical compounds [87]. In the experiment, peppermint oil reduces the effectiveness of amphotericin against *Candida albicans*, but enhances the antibacterial effect of nitrofurantoin against enterobacteria [3]. In the experiment, intragastric administration of mint oil (100 mg/kg) daily for 28 days caused histopathological changes in the white matter of the brain in rats, while behavioral disorders and the appearance of clinical symptoms were not established [98, 103].

When the therapeutic dosages of mint oil and menthol are exceeded, the following are described in the literature: dyspepsia, skin rashes, itching, bradycardia, headache, muscle tremor and ataxia [28, 32, 45, 62, 67, 68, 82, 84, 103]. When using drugs containing menthol or mint oil, which do not have a special film coating, heartburn is possible, especially in patients suffering from reflux esophagitis [28, 41, 103]. Recurrent myalgias have been noted with oral intake of essential oil [103, 104]. Other types of side effects of mint and individual biologically active substances from it, contraindications for use and possible risks when used as part of finished drugs and food products are presented in Table. 1 (column 4).

Common chicory (*Cichonum intubus* L.). Toxic effects when taking chicory and preparations based on it are not described.

St. John's wort, or common (*Hypericum perforatum* L.), St. John's wort

spotted or tetrahedral (*Hypericum maculatum* Crantz (*H. quadrangulum* L.). Extract John's wort is a strong inducer of CYP3A4 in hepatocytes and enterocytes of the intestine, which has been shown in the experiment in vitro (on human liver microsomes), in vivo (mice, rats, rabbits, minipigs) and in the clinic [3]. The combined use of St. John's wort extract with CYP3A4 substrate drugs leads to a decrease in the effectiveness of these drugs due to the acceleration of their biotransformation (combined oral contraceptives; immunosuppressants; statins; slow calcium channel blockers, some cytostatics). By inducing CYP2C9, St. John's wort extract is able to reduce the concentration of CYP2C9 substrate drugs: non-steroidal anti-inflammatory drugs, sulfonylurea derivatives, fluvastatin, etc., which is especially clinically significant for oral anticoagulants (weakening of the effect). Inducing a number of other enzymes

When the extract is used together with antidepressants of the serotonin reuptake inhibitor group, manic symptoms may appear [3]. If the treatment is carried out outside medical supervision, then the combination of St. John's wort extract with other standard antidepressants (tricyclic antidepressants or fluoxetine, etc.) is also not recommended [103].

It is not recommended to take St.

Based on the analysis of 29 reliable publications of the results of drug interaction studies of St. John's wort extract with various classes of drugs, Barceloux DG compiled a summary table and an overview suitable for assessing the possible risks of using St. John's wort extract [28].

The following side effects have been proven: photodermatitis, fatigue (up to 5%), headache (up to 7%), dysfunction of the gastrointestinal tract [3]. Photosensitivity analysis showed that the threshold for increased risk was at the level of a daily dose of 2–4 g of the extract (approx. 5–10 mg of hypericin) [28, 95].

With prolonged use, drugs cause persistent narrowing of the lumen of blood vessels, which can lead to the development of atherosclerosis and arterial hypertension [7, 8]. After a 3-week intake of herbal infusion, an increase in the concentration of potassium and sodium ions in the blood serum was noted simultaneously. Pronounced changes develop on the 8th week of administration: blood clotting and blood glucose levels increase, electrolyte balance is significantly disturbed [7].

When eliminated through the kidneys, drugs can irritate the renal parenchyma, provoking an exacerbation of chronic kidney disease. It is not recommended to take as the only component in glomerulonephritis, however, it is allowed to use as part of fees [7]. The drugs have a cholekinetic effect, therefore they are contraindicated in cholelithiasis. They can cause discomfort in the area of the liver and gallbladder, bitterness in the mouth, loss of appetite [7].

In women, a large number of drug interactions with drugs and other products of therapeutic and prophylactic properties based on St. John's wort have been identified [97]. There are reports of the appearance of signs of virilization in them while taking drugs [7]. According to some reports, the negative effect of drugs on the cells of the mucous membrane of the gastrointestinal tract can initiate the development of neoplasms, the effect on skin turgor - the appearance of wrinkles [7].

Terpene derivatives can increase the sensitivity of patients to various chemical compounds [87]. Hypericin caused severe skin photosensitivity (in clinical trials in HIV-infected individuals) at doses up to 0.5 mg/kg twice a week in 11 of 23 patients [28, 49]. The toxic reaction manifests itself in the form of an erythematous rash. Featured

as well as other adverse reactions [28].

Hyperforin is responsible for the activation of the CYP3A4 isoenzyme (when taking St. It is important that administration for 3 days does not lead to clinically significant changes in CYP3A4 or CYP2D6 activity [28, 65], but a 14-day course at a dose of 900 mg of the extract per day reduces the bioavailability of a number of drugs already by 39% [28, 101]. Moreover, the induction of CYP3A4 after oral administration is higher than after intravenous administration [28, 36]. Hyperforin also causes the induction of CYP2C19, which catalyzes the metabolism of tricyclic antidepressants [28, 55]. The interaction of St. John's wort and digoxin depends on the dose and method of preparation of the St. John's wort extract, more precisely, on the concentration of hyperforin [28, 72].

With prolonged use of St. John's wort:

- tannins can cause atrophy of the gastric mucosa, reducing its secretory function, contribute to the occurrence of constipation [7];
- anthracene derivatives - irritation of the intestinal mucosa, diarrhea, abdominal pain [8].

With uncontrolled use of St. John's wort in high doses, hyperoside (quercetin glycoside) can provoke heart rhythm disturbances and blood pressure fluctuations [7]. Other warnings and contraindications to the use of St. John's wort are presented in Table. 1 (column 4).

Horsetail (*Equisetum arvense* L.). According to the European Commission E [op. by: Bulaev, 2013], side effects from the use of the herb and its interactions are not described.

According to other sources, horsetail herb preparations can irritate the kidney parenchyma, and therefore are contraindicated in pregnancy [12, 103]. The uterotonic effect of the methanol extract of the herb was revealed in experiments on an isolated preparation of the uterus of female rats at a concentration of 5 mg/ml in vitro [76, 103]. The methanol extract of the herb at an average effective dose of 20 µg/ml caused a cytotoxic effect on the human leukemia cell line (L1210) [60, 103]. An aqueous extract (10%) and a methanol extract at a concentration of 50 µg/ml did not show a cytotoxic effect on HeLa cells and CA-9KB cell culture, respectively [25, 77, 103].

The diuretic effect of horsetail is a consequence of irritation of the epithelium of the renal tubules, which causes a number of contraindications for use, in particular, chronic kidney disease in the acute stage, as well as severe heart failure [7]. However, in an open uncontrolled clinical study [14, 103], on the contrary, a positive effect was obtained (increased diuresis when taking grass juice at a dose of 1 tablespoon 3 times a day) in patients with heart failure and edema. In the same study, an infusion (15 g of raw material in 180 ml of water) was used at a dose of 1 tbsp. l. every 2 hours) with dropsy; diuresis increased in more than 50% of patients [14, 103].

When keeping rats for 14 days on a cholesterol-enriched diet (0.5% cholesterol and 0.15% sodium cholate), with the addition of 4% horsetail grass powder, the appearance of dermatitis in the neck, head and back was recorded in 65% of animals. With a normal diet, this effect was not found [52, 103]. Antithiamine (Vit. B1) activity has also been established for horses fed with dried horsetail grass in an amount of 20% or more of the weight of the total diet for 2–5 weeks (equisetosis) [38, 66, 103]

Horsetail is not recommended to be added to a bath for skin diseases, infectious diseases, heart failure and arterial hypertension without consulting a doctor [46, 103].

When studying the toxicity of certain groups of horsetail biologically active substances, it was shown that flavonoids have a dose-dependent effect on the immune status: in small doses, they slightly stimulate the immune response, and in high doses, they can cause immunosuppression [7]. Alkaloids of the nicotinic and pyrimidine series in combination with other biologically active substances of horsetail herb can be toxic: children who chewed the stem of the plant showed symptoms of intoxication similar to nicotine poisoning [38, 103]. Therefore, in accordance with WHO recommendations, fresh and

dried herb and powders from it should not be used by nursing mothers and in pediatrics [103] due to the content of inorganic silicon components and alkaloids [38, 103].

Oats (*Avena sativa* L.). Side effects are not described. Oat preparations are not it is recommended to prescribe simultaneously with statins [3]. Oat grain can provoke non-immunological reactions due to histamine liberators and aflatoxins. Other types of side effects, contraindications for use and possible risks when using oats as part of finished preparations and food products are presented in Table. 1 (column 4).

Galega, or goat's rue medicinal (*Galega officinalis* L.). Grass enhances lactation, stimulates the secretion of sweat glands and glands of the mucous membrane of the urinary tract [8]. It also increases lactation in animals, although it is noted in specialized publications that cattle avoid eating galega when grazing [48].

The death of 38 sheep on a Belgian farm from the use of hay contaminated with galega grass is described. In sheep that survived the poisoning, repeated intake of the herb, even at low doses, caused abortion [42]. The toxicity of this plant for sheep is the highest compared to other animals (cows, goats, horses) [48]. In herbivores, toxicity depends on the time of grass harvesting (hay cutting). In the experiment, rabbits, dogs, hamsters, guinea pigs, and rats are insensitive to galega toxic substances [48, 58]. The sensitivity of people varies individually up to a dose of 25 g/kg of grass [48, 57].

Hypotensive and neurotoxic effects of the guanidine alkaloid galegin were shown. [56]. LD50 for grass in Wistar rats is more than 5 g/kg, in mice (subcutaneous injections of alcohol extracts from seeds and leaves) in terms of galegin sulfate LD50 77.5 mg/kg [48, 58].

Identification of promising plant species as sources of antidiabetic medicines and phytonutrients with minimal predictive allergic and other risks

Since the presence of even trace amounts of an allergen can cause the development of allergic reactions in sensitized individuals, the assessment of prognostic allergological risks is a necessary condition for the creation of effective and safe products based on medicinal plant materials (drugs, dietary supplements for food, specialized food products).

Taking into account the results of the assessment of data published in the literature, the analyzed risks of developing cross-allergic reactions and a comparative analysis with the official WHO/IUIS Allergen Nomenclature, two types of medicinal plants (common blueberry, stinging nettle) and 4 types of domestic large-tonnage medicinal plant raw materials can be recognized as the most promising : leaves (or shoots) of blueberry and leaves (or grass) of stinging nettle. And taking into account the possible cross-allergic reactions to the roots, leaves or herb of the nettle in the presence of an allergy to other plants of the Urticacea (Nettle) family [103], as well as contraindications to the use of nettle preparations with increased blood clotting [7, 8] and the specific taste of the extract from leaves (herbs) of nettle,

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conclusions

1. As a result of the information and analytical study, it is shown that when developing products based on herbal medicinal and food raw materials, it is mandatory to take into account possible allergological and other risks from the use of medicinal plants as ingredients of herbal preparations and phytonutrients in the composition of specialized food products.

2. Taking into account international recommendations on predictive safety assessment

herbal preparations and specialized food products, a preliminary informational assessment of the potential allergological risks of using 13 medicinal plants - promising sources of drugs and phytonutrients for specialized food products for patients with diabetes mellitus was carried out.

3. Of the 13 most used in traditional recipe guides of domestic medicinal plants (sources of phytonutrients) for the treatment of diabetes mellitus, the most prognostically safest in terms of allergological and toxicological risks of specialized food products with an optimized composition for patients with diabetes mellitus are leaves (shoots) of blueberry.

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Author's address

Doctor of Pharmacy, prof. Kiseleva T.L., Leading Research Center employee of the Federal Scientific Center for Nutrition, Biotechnology and Food Safety

KiselevaTL@yandex.ru

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