Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОБЗОРЫ

DOI: 10.19163/2307-9266-2023-11-5-399-411

Phenylpropanoids as a class of natural biologically active organo-protective compounds

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Received 25 Oct 2023 After peer review 24 Nov 2023 Accepted 15 Dec 2023

The aim of the work was to analyze the current research state of phenylpropanoids as a special specific class of biologically active compounds and the prospects for their use for the development of medicines and biologically active food additives.
Materials and methods. The scientific data for the period from 1968 to 2023 were studied in the databases of Scopus, ScienceDirect, PubMed, Google Scholar, e-library.ru, ResearchGate – a scientific information network. Herewith, the following keywords were used: "phenylpropanoids", "antioxidants", "hepatoprotectors", "immunomodulators", "organoprotectors", "anxiolytics", "adaptogens", "preventive medicine", "sanogenesis", "medicines", "biologically active food additives", "sports medicine" and their English-language analogues.
Results. This scientific research examines the main stages and results of studying the class of phenylpropanoids in the following aspects: a chemical structure and classification, biosynthesis and its role in the biogenesis of other classes of phenolic compounds, their distribution, biological and pharmacological activity in the plant world, the search for plant sources and their use in medicine and pharmacy. The existing and potential applications of phenylpropanoids for preventive and therapeutic purposes are discussed.
Conclusion. The analysis of the scientific publications on the pharmacognostic and biomedical studies of the medicinal plants containing phenylpropanoids, substantiates the expediency of considering them as an autonomous specific class of biologically active compounds. The organoprotective profile of their action and a wide range of specific pharmacological activities of phenylpropanoids are connected by common links of the sanogenesis in the "prooxidant–antioxidant" system. The choosing of promising plant sources for the development of medicines and biologically active compounds with specified properties is justified from the dependence position of "chemical composition – structure of compounds – spectrum of activity".
Keywords: phenylpropanoids; antioxidants; hepatoprotectors; immunomodulators; organoprotectors; anxiolytics; adaptogens; preventive medicine; sanogenesis; medicines; biologically active food additives; sports medicine
Abbreviations: ROS – reactive oxygen species; BAFA – biologically active food additives; BAC(s) – biologically active compound(s); MPRMs – medicinal plant raw materials; MR – medicinal remedy; CNS – central nervous system.

Фенилпропаноиды как класс природных биологически активных соединений – органопротекторов

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Получена 25.10.2023 После рецензирования 24.11.2023 Принята к печати 15.12.2023

For citation: V.A. Kurkin, N.R. Varina, E.V. Avdeeva, I.V. Ruzaeva. Phenylpropanoids as a class of natural biologically active organo-protective compounds. *Pharmacy & Pharmacology.* 2023;11(5):399-411. **DOI:** 10.19163/2307-9266-2023-11-5-399-411

Для цитирования: В.А. Куркин, Н.Р. Варина, Е.В. Авдеева, И.В. Рузаева. Фенилпропаноиды как класс природных биологически активных соединений – органопротекторов. *Фармация и фармакология.* 2023;11(5):399-411. **DOI:** 10.19163/2307-9266-2023-11-5-399-411

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

Цель. Анализ современного состояния исследований фенилпропаноидов как самостоятельного класса биологически активных соединений и перспектив их использования для разработки лекарственных средств и биологически активных добавок.

Материалы и методы. Были изучены работы за период с 1968 по 2023 гг. в базах данных Scopus, ScienceDirect, PubMed, Google Scholar, e-library.ru, научно-информационной сети ResearchGate. Для поиска были использованы следующие ключевые слова: «фенилпропаноиды», «антиоксиданты», «гепатопротекторы», «иммуномодуляторы», «органопротекторы», «анксиолитики», «адаптогены», «профилактическая медицина», «саногенез», «лекарственные препараты», «биологически активные добавки к пище», «спортивная медицина» и их англоязычные аналоги.

Результаты. В работе рассмотрены ключевые этапы и результаты изучения класса фенилпропаноидов в следующих аспектах: химическая структура и классификация, биосинтез и роль в биогенезе других классов фенольных соединений, распространение в растительном мире, биологическая и фармакологическая активность, поиск растительных источников и их использование в медицине и фармации. Обсуждены существующие и потенциальные возможности применения фенилпропаноидов в профилактических и терапевтических целях.

Заключение. Анализ научных публикаций по фармакогностическому и медико-биологическому изучению лекарственных растений, содержащих фенилпропаноиды, обосновывает целесообразность их рассмотрения как самостоятельного класса биологически активных соединений. Органопротекторный профиль действия и широкий спектр специфической фармакологической активности фенилпропаноидов связан общими звеньями саногенеза системы «прооксидант – антиоксидант». С позиции зависимости: «химический состав – структура соединений – спектр активности» обоснован выбор перспективных растительных источников для разработки лекарственных средств и биологически активных соединений с заданными свойствами.

Ключевые слова: фенилпропаноиды; антиоксиданты; гепатопротекторы; иммуномодуляторы; органопротекторы; анксиолитики; адаптогены; профилактическая медицина; саногенез; лекарственные препараты; биологически активные добавки к пище; спортивная медицина

Список сокращений: АФК – активные формы кислорода; БАД – биологически активная добавка к пище; БАС – биологически активное соединение(я); ЛП – лекарственный препарат; ЛРС – лекарственное растительное сырье; ЛС – лекарственное средство; ЦНС – центральная нервная система.

INTRODUCTION

The processes of biosynthesis in plants lead to the accumulation of primary and secondary metabolites, many of which have a high value for medical use. These include phenylpropanoids, which are aromatic, mainly phenolic compounds containing one or more fragments of phenylpropane (C_6–C_3) in their structure [1].

In the present, through the efforts of Russian and foreign scientists, a significant amount of data have been accumulated on the biologically active compounds (BACs) under discussion, including previously generalized and systematized ones in a number of monographs and review papers. They are mainly devoted to the consideration of phenylpropanoids as a class of chemical compounds of natural origin [2]. The current request of the scientific community is to proceed to the assessment of the current state of pharmacognostic and biomedical data, as well as prospects for the realization of the therapeutic and preventive potential of phenylpropanoids, based on existing knowledge on the chemical structure, physical and chemical properties, information on the chemical composition of medicinal plant raw materials (MPRMs), the accumulated experience in their medical use.

This review, from the standpoint of continuity in the accumulation of scientific knowledge based on the principles of evidence-based pharmacy and medicine, should serve as a guideline for the creation of organoprotective medicines and biologically active food additives (BAFAs) based on phenylpropanoids and their derivatives for the therapy and prevention of a wide nosological spectrum, including sports medicine.

THE AIM of the work was to analyze the current research state of phenylpropanoids as an autonomous specific class of natural compounds and the prospects for their use for the development of medicines and biologically active food additives.

MATERIALS AND METHODS

The analysis and systematization of the material was carried out using the scientific databases of Scopus, ScienceDirect, PubMed, Google Scholar, e-library.ru, as well as the ResearchGate scientific information network (56 publications out of more than 350 articles were selected as the most significant). The time period of the published scientific data coverage was the interval from 1968 to 2023. The information search was conducted using the following keywords: “phenylpropanoids”, “antioxidants”, “hepatoprotectors”, “immunomodulators”, “organoprotectors”, “anxiolytics”, “adaptogens”, “preventive medicine”, “sanogenesis”, “medicines”, “biologically active food additives”, “sports medicine” and their Russian-language analogues.

RESULTS AND DISCUSSION

Historical information

The diverse study of phenylpropanoids and their derivatives by the professional scientific community has been carried out over the past 70–80 years [1, 3–5].

DOI: 10.19163/2307-9266-2023-11-5-399-411

The name “phenylpropanoids”, as well as such concepts as “phenylethanoids” and their derivatives (hydroxyphenylpropanoid and phenylethanoid glycosides), “simple phenolic compounds”, “phenol carboxylic acids”, “conjugates of caffeic acid” and a number of other designations have been widely used in the scientific literature since the 1950s of the last century and often overlapped in terms of meaning (sometimes with the substitution of concepts: e.g, hydroxycinnamic acids were called carboxylic acids), which required a harmonious chemical systematization from the structural features standpoint of the above-mentioned groups of compounds. The chemical classification of compounds of the phenolic nature, taking into account the organic bond between the compounds and the sequence of their biosynthesis, appeared only at the turn of the century and is currently fundamental in modern pharmacognosy [1]. Actually, the classification of phenylpropanoids themselves as compounds based on the phenylpropane fragment, as well as their position in the general classification of compounds of the phenolic nature in the logic of biosynthesis and complication of the structure of the carbon skeleton, is a fundamental position [1].

In the 2000s, in the continuation of the fundamental work on the study of phenylpropanoids based on the study of biomedical properties and the establishment of a characteristic activity profile, the understanding of phenylpropanoids expanded to the designation as an autonomous specific class of natural BACs. At the same time, a systematic approach to the study of a chemical composition, the standardization and search for perspective MPRMs was developed from the identified spectrum standpoint of the pharmacological activity of medicinal plants containing phenylpropanoids. Finding of new properties of this class of BACs, including their role for plants themselves, for example, as UV protectors (which has not yet been transferred to the medical practice) [6, 7], the data on prevalence, as well as the overlap of scientific fields: the data on the support of the homeostasis system, and, in particular, immune homeostasis, understanding of the mechanisms of pathogenesis and sanogenesis, and pharmacognostic knowledge itself have significantly expanded the range of ideas about the possibilities of using phenylpropanoids, as evidenced by the worldwide publication flow [8–11].

At the same time, in parallel with the successes in pharmacognosy, the fundamental foundations of the vital activity of the body, the homeostasis system, were investigated , which, in turn, served as a methodological substantiation for studying biomedical properties of a new class of BACs. The last decades of the previous century and the first decades of the XXI century were marked by a deep, at the molecular level, study of the “prooxidant–antioxidant” system, immune homeostasis, modulation of control signals, a protein-protein interaction and made it possible to deepen the understanding of the body as an integrated system. In particular, in a broad sense, damaging factors of the external and internal environment, of the infectious and non-infectious nature cause a set of responses at different levels of the organization of living matter, forming etiopathogenetic clusters [12].

The body responds to this set of pathological reactions (links of pathogenesis) by activating the corresponding links of sanogenesis. The organism is not always able to cope on its own, which leads to the formation of pathological conditions and diseases of various systems and organs, which necessitates a comprehensive confrontation, including medicinal organoprotective effects. It should compensate for the insufficiency of endogenous bioregulation and protection factors (specific and non-specific), depletion of the body’s antioxidant potential, and adaptive capabilities [12–14]. The majority of research teams consider the therapeutic and prophylactic potential of phenylpropanoids in this direction, as well as types of specific pharmacological activity related through the links of sanogenesis.

The works by mainly Russian scientists in recent decades in relation to more than 20 plant species containing mainly (as the leading group of BACs) phenylpropanoids and their derivatives have led to the receipt of valuable applied data and a line of drugs. The antioxidant, hepatoprotective, neurotropic and immunomodulatory effects were specified for isolated individual compounds of the phenylpropanoid nature and total native complexes of active substances depending on the structure of the active ones [15–18]. It has been proved that the spectrum of this activity directly depends on belonging of compounds to the classification groups of phenylpropanoids (derivatives of cinnamon alcohols, acids, neolignans, lignans, flavolignans, etc.) and the features of the chemical structure: an antioxidant activity and an immunomodulatory effect are common characteristic features of the BACs class. The adaptogenic properties are also, in various aspects, inherent in most of the isolated and studied compounds and the total native complex of plant active substances, but the CNS stimulating properties are most pronounced; they are more characteristic of cinnamon alcohols derivatives for both simple and complex phenylpropanoids. Flavolignans are the leaders

ISSN 2307-9266 e-ISSN 2413-2241

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in the hepatoprotective activity. These data from the perspective of the relationship of "chemical structure – pharmacological action – application" regarding the effect of phenylpropanoids on the links of the antioxidant protection, modulation of the immune response and, in general, the activation of nonspecific resistance and adaptation systems of the body, made it possible for the scientists to justify the rational use of the appropriate plant sources to obtain a variety of phytosubstances for clinical use and prevention of a large number of diseases [19–22]. I.e., in our opinion, are the current results of today, as well as the starting point for further works.

Let's consider various aspects of modern ideas about phenylpropanoids as a basis for the realization of further prospects for their rational use in medicine and pharmacy.

Concept of phenylpropanoid class

Phenylpropanoids are quite common in the plant world, but since they were introduced into pharmacognosy relatively recently as an independent class of natural BACs, these compounds can be considered, despite a long history of interest in them, as a relatively young class of secondary metabolites [1, 2]. The structural features and physical and chemical properties of these compounds have been studied in depth by the efforts of Russian and foreign scientists. In particular, for phenylpropanoids, it has been proved that a nuclear magnetic resonance (NMR) spectroscopy is the most important method for establishing their chemical structure, which, together with a mass spectrometry, an UV spectrometry and chemical reaction results, make it possible to unambiguously establish their structure. This way, on the ^{1}H-NMR spectra on the scale of chemical shifts in the range of 6.7–7.3, there are resonance signals of aromatic protons, and in the range of 8.5 and 6.3 m.d. of aliphatic protons [1, 5].

A classification of phenylpropanoids and their derivatives based on the data about the structure of compounds and their biosynthesis was proposed; that led to a revision of the entire chemical classification of phenolic compounds in 1996. In accordance with this classification, phenylpropanoids should be isolated into a separate class of BACs and also divided into subgroups within the class according to the biosynthesis products on several grounds: according to the number of phenylpropane fragments, into simple and complex (lignans); depending on the functional group of the propane fragment, several more groups are divided, herewith, cinnamon alcohols and cinnamon acids have the highest value of the medical and preventive importance. There are also organically related small groups of BACs, as a rule, formed by an oxidative combination of the phenylpropane fragment with other classes of compounds (flavolignans, coumarinolignans, xanthonolignans, alkaloidolignans). Besides, there are some other classification grounds [1].

All these are fundamentally important from the point of view of establishing dependencies of "structure – activity", including a biological activity and pharmacological effects of both the initial compounds and their derivatives. The studies by foreign scientists show that glycosides of p-coumaric, caffeic and ferulic acids, which are the most important metabolites of natural BACs, have a high metabolic activity. In the present study, cinnamon alcohols were considered, then, according to the results of the research, it was found out that the reactivity increases in the following line: cinnamon alcohol – *p*-coumaric alcohol – coniferyl alcohol – synaptic alcohol, since in this line the number of functional groups involved in the oxidative combination reactions, increases. This process results in the formation of lignoid and lignan molecules. As discussed, these complex phenylpropanoids based on coniferyl or synaptic alcohols are most often found in nature [1, 11, 21].

Biosynthesis of phenylpropanoids and their biogenetic role in synthesis of other phenolic compounds, distribution in plant world

Simple phenylpropanoids, primarily *p*-coumaric (hydroxycinnamic) acid, are formed by the shikimate pathway from phenylalanine and tyrosine, as well as from intermediate compounds along the way of their formation (quinic and shikimic acids). The representatives of this BACs class are formed from hydroxycinnamic acid under the influence of hydroxylating (cinnamic acid hydroxylase and polyphenol oxidase) and methylating enzymes with corresponding functional groups [1, 4].

Biosynthesis of simple phenylpropanoids can be considered as the first step in the synthesis of a number of phenolic compounds belonging to other autonomous classes of phenolic compounds. Thus, phenylpropane fragments are found in the structure of a number of simple phenolic compounds, coumarins, flavonoids, tannins of a condensed nature, which indicates the role of phenylpropanodes as a biogenetic precursor. Herewith, as a result of the chalcon synthetase reaction, hydroxylation and isomerization reactions, condensation, etc., in the formation of carbon skeletons of these autonomous classes and groups of phenolic compounds, biosynthesis processes follow the acetate–shikimate pathway. With regard to the combinations of

DOI: 10.19163/2307-9266-2023-11-5-399-411

phenylpropanoids with each other and with substances of a different nature (not only phenolic), lignans and lignoids are isolated and united by the general concept of complex phenylpropanoids. As previously stated, their biosynthesis is based on an oxidative combination, mainly on the propane fragment of the molecule from the phenylpropanoid side [4, 5, 11].

Herewith, to date, the literature data and this research show that phenylpropanoids are most widely distributed and accumulated in significant amounts (up to 3–4%) in the plants of the following families: *Asteraceae*, *Araliaceae*, *Crassulaceae*, *Salicaceae*, *Plantaginaceae*, *Lamiaceae*, *Oleaceae,* etc. [2, 5, 23]. At the same time, the relationship between taxonomic units and classification subgroups of phenylpropanoids has not been yet revealed. Probably, as biogenetic precursors, especially the progenitors of the series of cinnamic acids and alcohols, phenylpropanoidshave have already been identified and are expected in all plants containing a diverse range of compounds of the phenolic nature. The only open question remains about the final accumulation of secondary metabolites in the plant raw materials. There are examples of finding the same phenylpropanoid in the representatives of taxonomically distant families: the synaptic alcohol glycoside under the names of syringin and eleutheroside was isolated at different times and independently named by researchers in accordance with the MPRMs sources – the bark of lilac (*Syringa vulgaris* L.) and the rhizomes of eleutherococcus senticocus (*Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim.), respectively. There are examples of only a single finding of complex phenylpropanoids in specific plants – for example, flavolignans of *Silybum marianum* (L.) Gaertn.; there are isolated cases of the detection of alkaloidolignans and xanthonolignans. However, it is too early to put an end to this issue, taking into account the biogenetic role of phenylpropanoids [2].

From the whole variety, the plants that have been studied quite deeply to date, are, in the authors' opinion, represented by the following species of MPRM: milk thistle fruits – *Silybum marianum* (L.) Gaertn., rhizomes with roots of Leucea safflower (Rhaponticum safflower) – *Rhaponticum carthamoides* (Willd) DS, herbs of *Echinacea purpurea* (L.) Moench., the *Asteraceae* family; rhizomes with roots of Eleutherococcus prickly – *Eleutherococcus senticocus* (Rupr. et Maxim.) Maxim., the *Araliaceae* family; rhizomes and roots of *Rhodiola rosea* L., the *Crossulariaceae* family; bark of willow species – *Salix species*, the *Salicaceae* family; lemon balm – *Melissa officinalis* L., the *Labiaceae* family; common lilac – *Syringa vulgaris* L., the *Oleaceae* family; Chinese lemongrass – *Schizandra chinensis* (Turcz.) Baill., the *Schizandraceae* family) [23–25].

Focusing on this sample group of plant sources from the standpoint of the scientific justification for the development of MPs and BAFAs in the following aspects – their chemical composition, approaches to the isolation and the analysis of the active substances (the target groups of BACs and the leading group – analytes), enhances solving the problem of standardization, substaniation of the application in medical practice [26].

Phytochemical aspects of studying and solving standardization issues of selected species

Among the science-intensive but absolutely necessary research stages from the point of view of understanding the potential of MPRMs, their standardization and the production of various phytosubstances, is the study of their chemical composition. In case of the isolation of phenylpropanoid compounds and their derivatives in individual forms, the task seems complex and multistage: not all compounds are crystalline, there are many concomitant substances in their polarity and chromatographic behavior; the substances react with ethyl alcohol, and there is a number of other difficulties. However, by now, the scientists have developed fundamental schemes for isolating a group of cinnamon alcohols and cinnamon acids. The concentration range of ethyl alcohol is 40–70% (according to the authors' observations, ethyl alcohol is preferable at 70%, especially if the task is to extract the majority of compounds of a phenolic nature as much as possible). The adsorption column chromatography is used to separate the initial extraction. Silica gel and polyamide are used as a sorbent (according to the authors' observations, there are quite low sorbent layers, herewith, the diameter of the sorbent layer is a priority), the solvents and their mixtures in the increasing polarity in a row (*n*-hexane, chloroform, ethyl alcohol, water) are used as a system of eluents. The obtained target fractions (TLC control) are subjected to rechromatography, crystallization and recrystallization from the appropriate solvents. In the case of a derivative of hydroxycinnamic acids (non-crystalline compounds), sephadex (molecular sieves) is additionally used. Thus, the state standard samples (SSSs) of cinnamon alcohols of a crystalline nature – rosavin, triandrin, syringin, silybin – were obtained, whereas individual compounds are representatives of the group of cinnamon acids (caffeic, rosemary, chicory and other acids) and have the status of working standard samples only [1, 2].

Modern instrumental capabilities greatly simplify

ISSN 2307-9266 e-ISSN 2413-2241

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the routine practice of isolating and purifying the compounds – most phenylpropanoid glycosides have been obtained to date using preparative HPLC. However, the delicate aspects of studying a full spectrum of BAC plants, as well as obtaining standard substances, still require skilled, delicate workmanship on the separation of substances by rechromatography and recrystallization of substances from different solvents [1].

The TLC analysis with using the systems "chloroform–methanol–water" (26:14:3) or "chloroform–ethanol–water" (26:13:4), has proven itself well for the detection of phenylpropanoids in MPRMs and extraction (galenic) preparations, herewith, the R_f index is in the range of 0.4–0.5. The subsequent viewing of chromatographic plates is carried out in the UV at wavelengths of 365 and 254 nm. Phenylpropanoids have a bluish-violet fluorescence (the irradiation at 365 nm) or, in the presence of free phenolic hydroxyl groups, they are found in the form of purple–crimson spots (the irradiation at 254 nm). For the compounds with a low polarity, in particular flavolignans, an effective separation is achieved in the system of "cyclohexane–acetonitrile" (6:4). Viewing in the UV light at 254 nm makes it possible to identify purple spots in the analytical area of the chromatogram. In addition to the TLC analysis, the UV spectrum is actively used for the purposes of a qualitative analysis of MPRMs and preparations. It is characteristic of cinnamon alcohols derivatives – a single absorption maximum is observed in the range of 250–270 nm, the exact value depends mainly on the presence of the amount of free hydroxyl radicals in the phenolic fragment; several absorption maxima are characteristic for the derivatives of cinnamon acids – at 235, 242, 325–330 nm (basic) [2, 27].

The described characteristics of the chromatographic behavior, including those implemented in the HPLC analysis [28, 29], and the data from the electronic spectra of phenylpropanoids serve as the basis for the development of unified analysis methods for MPRMs and preparations. They are reflected in the regulatory documentation (relevant sections of the State Pharmacopoeia of the Russian Federation of recent editions), and in the search for perspective MPRMs for the development of MPs and BAFAs, it is confirmed by numerous publications on determining the amount of hydroxycinnamic acids and derivatives of cinnamon alcohols [30–32].

Herewith, in the proposed methods of qualitative and quantitative analyses, the standard substances are used; their development is traditionally considered one of the most science–intensive tasks in pharmacognosy. To date, the methods for obtaining standard substances have been proposed. The sequence is as follows:

– Determination of dominant and diagnostically significant substances in the course of phytochemical studies of MPRMs are potential candidates for the status of standard substances;
– Assessment of the possibility of their isolation in an individual form – the task is quite facilitated in case of the substance crystalline nature (both for purification of the compound with minimizing losses and a further study of physical and chemical characteristics, the melting point can be used as one of the criteria for the purity of the compound and a number of other advantages);
– Determination of physical and chemical constants of the compounds, the development of methods for evaluating their quality indicators.

The next stage is the use of standard substances for analytical purposes – the choice of analytical methods and the development of methods for qualitative and quantitative analyses of the leading group of compounds [1, 2].

In particular, the following approaches for the discussed priority group of plant sources are justified: the leading group of BACs for MPRMs and preparations of *Rhodiola rosea* L., *Eleutherococcus senticocus* (Rupr. et Maxim.) Maxim., *Syringa vulgaris* L. are glycosides of cinnamon alcohols. Accordingly, the standard substances for them are SSSs (rosavin and syringin; the quality assessment of MPRMs and preparations of *Silybum marianum* (L.) Gaertn. should be carried out according to the amount of flavolignans – SSS silybin is proposed, and the determination of the amount of flavolignans is carried out in terms of silybin; in relation to the MPRMs and preparations of *Melissa officinalis* L. and *Echinacea purpurea* (L.), hydroxycoric acids are the analytes. Therefore, using appropriate working standard samples, a conversion to rosemary or chicoric acid is carried out, but the replacement with caffeic acid is possible: it is the leading and analyzed group for echinacea and analyzed for melissa (essential oils) [2, 33–34].

Biomedical properties of phenylpropanoids and theoretical prerequisites for their use in medical practice

When it is necessary to select a potential range of medicinal plants that could serve as a source of therapeutic and prophylactic agents to be used in a wide nosological spectrum of diseases. It is also important to involve BACs, activating or modulating links of sanogenesis in an increased physical and

DOI: 10.19163/2307-9266-2023-11-5-399-411

intellectual stress associated with stress factors, including a chronic fatigue, a depletion of internal reserves of the antioxidant protection, the adaptation mechanisms [14, 26].

The study of antioxidant, hepatoprotective, adaptogenic, immunomodulatory and neurotropic properties of various phytosubstances and individual phenylpropanoid compounds and their derivatives, as well as a proven safety (a class of low-toxic compounds) make it possible to classify them as valuable organoprotectors. Herewith, for specific purposes, it is important to take into account the profile of a specific pharmacological activity and, based on knowledge of the chemical composition, to study the dependences of "structure of the compound – biological activity" and "chemical composition – pharmacological effect". Such work has been carried out by many domestic and foreign scientists, which today allows us to group plant sources containing phenylpropanoids and their derivatives according to the prospects of use for therapeutic and prophylactic purposes [2, 23].

In terms of the effect on ROS and PLP processes, the negative consequences of these processes (free radical traps, activators of a number of antioxidant enzymes), the antioxidant activity manifests itself best of all in the substances with the largest number of phenolic –OH и $–OCH_3$ groups, as well as in the presence of a system of conjugated double bonds. Any features and transformations of the propane fragment do not contribute to the effect. In other words, the antioxidant activity can be considered a characteristic property of all phenylpropanoids. The priority group of the substances are *Silybum marianum* (L.) Gaertn. Flavolignans. Herewith, the plant's phytosubstances are more active in the natural complex of flavolignans+flavonoids. The highest hepatoprotective activity was also noted for them [35].

The immunomodulatory activity was noted in all phenylpropanoids; this can be explained, at least, by the general beneficial antioxidant effect, including that on the immune system. Based on this, an immunocorrective effect should be expected from all the discussed objects to some extent (the effect on the cellular and humoral link of the immunity, activation of phagocytosis have been described). A clear "structure–activity" relationship has not yet been revealed. At the same time, the preparations of *Echinacea purpurea* (L.), in the herb of which chicory acid and other conjugates of caffeic acid accumulate, are recognized leaders in the immunomodulatory action. Plant heteropolysaccharides with immunostimulating properties make a certain contribution to the immunotropic effect [22, 36, 37].

Toning and adaptogenic properties are most inherent in the group of cinnamon alcohols, which are the main active ingredients of *Rhodiola rosea* L., *Schizandra chinensis* (Turcz.) Baill., *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim., *Syringa vulgaris* L. raw materials. There is the following connection in this group: the glycosides are more active than the corresponding aglycones [38–41]. Due to the content of ruzavin and other simple and complex phenylpropanoids, the widest spectrum of a neurotropic activity is inherent in the rhodiola rosea preparations. Phenylethanoid salidroside (an actoprotective activity) also makes a certain contribution there [38, 42].

Anabolic and general stimulating properties are associated with the content of ecdysteroids in the *Rhaponticum carthamoides* (Willd), which is interesting for the training of athletes and people leading an active lifestyle [43–45].

Cinnamic acids do not have an activating effect on the central nervous system, but they have another valuable property – they are anxiolytics (in particular, *Melissa officinalis* L. and *Mentha piperita* L.) [46–48].

To obtain medicines from plant raw materials containing phenylpropanoids, scientists use different ways. The traditional and at the same time modern approach is the extraction of the native range of active substances [2, 49, 50]. At the same time, the researchers take into account the biosynthetic conditionality of the joint presence of phenylpropanoids and other groups of phenolic compounds interrelated with them (coumarins, flavonoids, tannins, etc. classes) in medicinal plants, which is also an important factor for choosing a particular plant object as a source of BACs for the creation of new MPs and BAFAs. The reason for this is the fact that native combinations of BACs of various classes as target groups of active substances have the advantage of a complex effect. They maintain the normal state and work of the functional systems of the body exposed to various negative factors of the external and internal environment, infectious and non-infectious nature, since in many cases there is a synergistic effect of different types of a biological activity that are inherent in one type of plant raw materials and act co-directionally on the body (rather than their algebraic sum), and, accordingly, it leads to an increase in the main pharmacological effect [22–25].

In addition, it seems promising to create complex phytosubstances based on combinations of plant raw material species – their total extracts and purified amounts of compounds, as well as individual substances of plant and other origins. These are vitamins and vitamin-like substances, amino acids, macro- and microelements, organometallic compounds and a

ISSN 2307-9266 e-ISSN 2413-2241
Scientific and Practical Journal
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number of other valuable ingredients and conditionally auxiliary substances. This approach, starting from the traditional production of extraction preparations, is now most actively developing in the preventive direction, in the dietary supplement sector [20, 26, 49].

Along with extraction methods for obtaining medicines, a biotechnological approach is also used, especially if there is a goal to increase the efficiency of obtaining specific active substances in total extracts or to obtain them individually. The approach seems relevant, for example, for such a rare and valuable plant as *Rhodiola rosea* L. (also called the "Golden root"), as well as closely related species (due to their high costs, laboriousness of the process of a preparative separation of the native BACs range or the isolation of individual natural compounds) [33, 42, 51, 52]. There are also attempts to obtain derivatives and other products of the phenylpropanoid compounds transformation by synthesis and semi-synthesis methods [23, 31]. E.g., the production of a water-soluble salt, silybin hemisuccinate, which, when injected, had a powerful antitoxic effect on isolated pale toadstool poisons in animal experiments [2].

Development of medicines and dietary supplements based on phenylpropanoids

As described in the scientific works by numerous authors, medicinal plants containing phenylpropanodes are a valuable source for the production of medicinal products and dietary supplements for the prevention and treatment of a wide nosological spectrum of diseases caused or followed by an imbalance of the prooxidant–antioxidant system. A shift in the equilibrium towards the prooxidant is observed with the depletion of the internal links of enzymatic and non-enzymatic antioxidant protection. One of the common links in the pathogenesis of a wide nosological spectrum is the free radical mechanism of damage to cell membranes. Herewith, an excessive amount of free radicals is formed in the body, in particular, ROS, the body loses its ability to maintain the balance of free radicals, which leads to the cell damage, the formation of pathological processes, an oxidative stress and various clinical manifestations (such as disorders of the normal functioning of the nervous, cardiovascular, hepatobiliary systems, a decrease in specific and nonspecific resistance of the body, the acceleration of the aging process and an increasing threat of oncopathology). In this case, while preventing the negative effects of free radicals, phenylpropanoids and their derivatives, acting as a «free radical trap», ROS and other damaging agents on body cells, enhance the body's own antioxidant defense and create favorable conditions for the formation of an effective immune response [12–14, 17].

All the types of MPRMs considered in this review are characterized by an antioxidant effect, which is considered as a key factor in ensuring the organoprotective effect of MPs and BAFAs based on them.

A number of the following examples, depending on the previously considered structural features of phenylpropanoids and their derivatives, have, along with a common antioxidant link, effects and narrower fields of application. The authors consider this spectrum with an indication of the main active ingredients (they, respectively, are proposed as standard samples for solving the issues of standardization of MPRMs and related drugs):

- *Rhodiola rosea* L. – a neurotropic and tonic activity (rosavin), an actoprotective activity (salidroside), an anticancer effect (lignan lariciresinol) [38].
- *Schizandra chinensis* (Turcz.) Baill. – stimulating the CNS and a general toning effect (γ-schizandrine) [41, 53].
- *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim. – a neurotropic activity (eleutheroside B), including a stimulating effect on the CNS; an immunomodulator [39, 50].
- *Syringa vulgaris* L. – a neurotropic activity (eleutheroside B, syringin); an immunomodulator [40, 54, 55].
- *Silybum marianum* (L.) Gaertn. – a powerful hepatoprotector (silybin, silidianin, silicristine, dehydrosilibin, and other flavolignans); an immunomodulator [35].
- *Echinacea purpurea* (L.) Moench. – an predominantly immunomodulatory effect (chicory acid and echinacoside) [36, 37].
- *Rhaponticum carthamoides* (Willd) DS – a general tonic, a CNS stimulating agent with an anabolic activity, anti-cancer against certain types of leukemia and adenosarcoma (ecdysteroids, lignans) [43, 56].
- *Melissa officinalis* L. – an anxiolytic effect and a less strong sedative; an immunomodulator (rosemary, caffeic and other hydroxycinnamic acids); antihistamine and antispasmodic effects (essential oils) [46, 48].

In particular, when studying the hepatoprotective properties of *Silybum marianum* (L.) Gaertn. flavolignans, the therapeutic effect of which is based on the antioxidant effect of BACs on various pathogenesis links and damage levels, was specified [35]. For the improved readability, hepatoprotective effects of phenylpropanoids, realized due to the antioxidant

DOI: 10.19163/2307-9266-2023-11-5-399-411

(H donors), antifibrotic (an interferogenicity), reparative (a stimulation of RNA synthesis) mechanisms of the action on some pathological links of the oxidative stress, described in a number of works, are reflected in the diagram for (Fig. 1) [12, 18, 23].

The targeted search and creation of safe drugs and dietary supplements with antioxidant effects that prevent a hyperlipoperoxidation, a destruction of cell membranes, and, at the same time, enhance the body's own enzymatic and non-enzymatic antioxidant systems, led to the creation of a series of effective drugs based on *Silybum marianum* (L.) Gaertn. flavolignans. The authors' data indicate that in comparison with the traditional approach of using a purified silymarin mixture of three dominant flavolignans, the entire native range of compounds has advantages. This is achieved by increasing a bioavailability and making the fullest use of the BACs antioxidant potential, since all flavolignans (more than 20 of them) have a hepatoprotective activity. These have been proven both in animal experiments and in the subsequent clinical use: a statistically significant increase in the activity of catalase and superoxidismutase and a decrease in the accumulation of malondialdehyde under the influence of the total extract – a native complex obtained on 80% ethyl alcohol, exceeding those indicators under the action of comparison drugs "Karsil" and "Legalon" [35].

With regard to the combination of antioxidant and immunomodulatory activities, a synergistic relationship can be traced in the antioxidant effect of phenylpropanoids and their modulating effect on the immune system: phenylpropanoids activate interferogenesis, phag ocytosis, including oxygen–dependent ones, and lead the parameters of the specific protection to the normal immune homeostasis [22]. Phenylpropanoids also modulate an immune surveillance in terms of the antiblastoma protection – these are mainly derivatives of cinnamon and synaptic alcohol. However, taking into account the not fully studied effect of antioxidant effects on the tumor growth, the issue of the application in oncology according to therapeutic schemes has yet to be subjected to the additional study. The preventive potential of phenylpropanoids is not in doubt yet [2, 23].

In terms of the secondary immunodeficiency conditions, *Echinacea purpurea* (L.) Moench. has proven itself well, but the condition for its effectiveness is to obtain the entire native range of BACs, in particular, the phenylpropanoids represented by conjugates of caffeic acid with sugars, quinic and tartaric acids. Chicory (2,3-O-dicofeylvinic) acid, which has immunomodulatory properties, and also serves as a working standard sample for analytical purposes, is especially valuable. Echinacoside also deserves attention, which, together with chicory acid, it also exhibits antibacterial properties against the coccal microflora (*Staphylococcus aureus* and *streptococcus*). The contribution of alkylamines enhances these types of activity, as well as the anti-inflammatory effect of plant preparations [2, 36, 37].

In the creation context of MPs and BAFAs of the adaptogenic action, they have justified themselves and have a potential to further reveal the beneficial properties of *Rhodiola rosea* L., *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim., *Syringa vulgaris* L., *Schizandra chinensis* (Turcz.) Baill., *Rhaponticum carthamoides* (Willd) DS, allowing the body to adapt faster due to the activation of the neuro-hormonal regulation. Indications for the use of MPs and BAFAs based on them, are: an astheno-vegetative syndrome, a relief of fatigue, hypoxia, a prevention and therapy of infectious and inflammatory diseases [38, 40, 41].

With regard to the tonic properties of plant adaptogens, it is generally believed that it is associated with an activating effect on the ascending reticular formation of the brain and the hypothalamic-pituitary-adrenal system. By inhibiting the enzyme catechol-O-methyltransferase (destroys adrenaline and norepinephrine), the dominance of the sympathetic nervous system increases. In this regard, it is advisable to limit the use of adaptogens and exclude their evening intake [12, 23]. Nevertheless, in order to achieve high athletic results during the active training, the potential benefits of the rational use are beyond any doubt [8, 19, 44, 45].

Among the adaptogen plants, *Rhodiola rosea* L. stands out for its wide range of neurotropic activities (a positive effect on cognitive abilities, antihypnogenic properties), as well as the rare property of normalizing a blood pressure; as noted, anti-cancer properties are also described. The reason for this range of effects lies in the unique chemical composition – simple phenylpropanodes rosavin, rosin and rosiridine, as well as the phenylethanoid salidroside contained, form adaptogenic properties together, including increased mental and physical activities, endurance; a slightly lower activity was observed in rosarin and cinnamon alcohol [24, 38].

Phytopreparations based on *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim. are characterized by a whole range of valuable properties (adaptogen, tonic and an immunomodulator), which is achieved by combining the synaptic alcohol glucoside syringin (eleutheroside B) and the diglucoside lignan syringarezinol (eleutheroside D) [39, 50].

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
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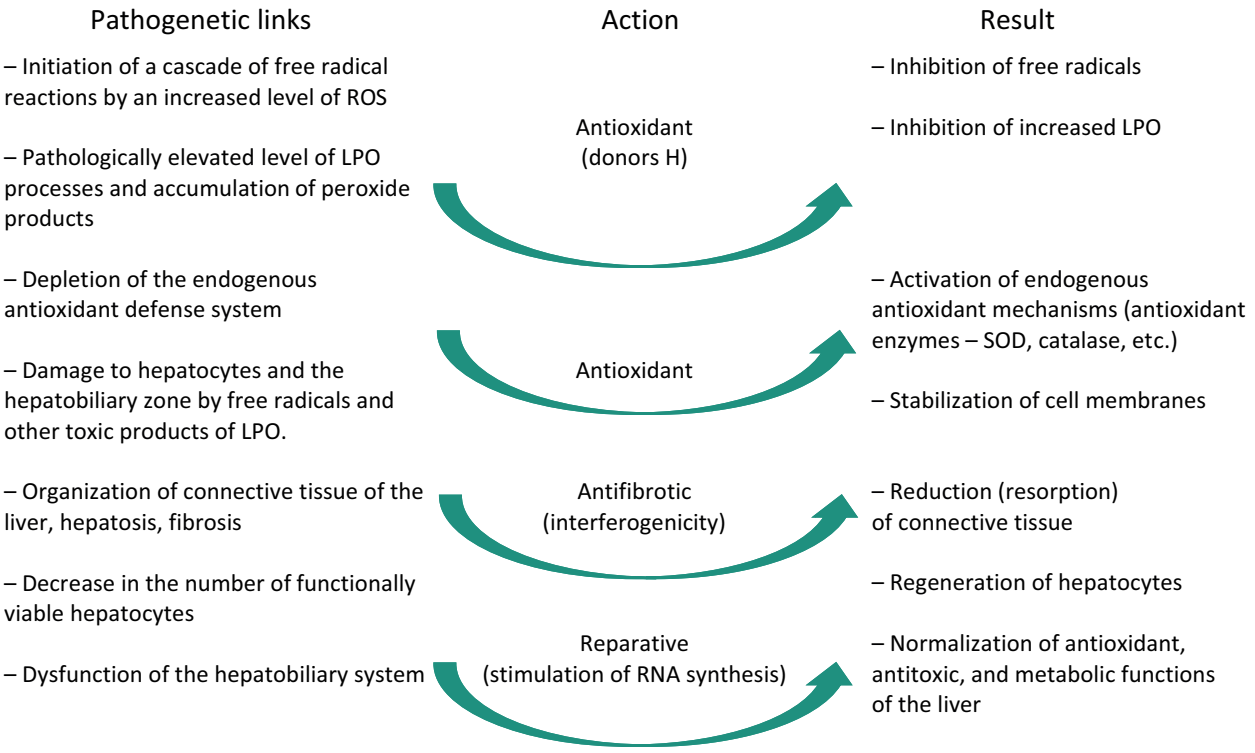

Figure 1 – Sheme of phenylpropanoids-hepatoprotectors action on some pathological links of oxidative stress
Note: ROS – reactive oxygen species; LPO – lipid peroxidation; RNA – ribonucleic acid; SOD – superoxide dismutase; H donors – hydrogen proton donors. The material for the scheme is adapted from [12, 18, 23, 35].

It should be also noted that the prospects for the development of phytopreparations based on the bark of *Syringa vulgaris* L., which also contains syringin, and is an order of magnitude higher than in the rhizomes of *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim. In addition, salidroside was also found out, and its contribution to the action of *Rhodiola rosea* L. preparations has already been mentioned: it ultimately enhances adaptogenic and tonic activities. A number of authors consider *Syringa vulgaris* L. bark to be a very promising source for the production of pharmaceutical substances [34, 40, 54].

Returning to the issue of the phenylpropanoids antitumor properties, it should be noted that the phytosubstances of *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim. and *Syringa vulgaris* L., as well as *Rhodiola rosea* L. and *Rhaponticum carthamoides* (Willd) DS, have antiblastoma properties. The basis for this is lignan – laryciresinol isolated from these species of *Eleutherococcus senticocus* (Rupr. Et Maxim.) Maxim., *Syringa vulgaris* L. and *Rhodiola rosea* L., for which antitumor properties were identified. Phytopreparations obtained from these plants can serve the purposes of a cancer prevention, especially for older people [25, 56].

Schizandra chinensis (Turcz.) Baill. contains phenylpropanoids represented by lignans, the most characteristic of it are schizandrin and ɣ-schizandrin. Along with the typical profile of its adaptogenic activity, the plant preparations (based on fruits and seeds) increase the blood pressure, increase the amplitude of heart contractions and reduce their frequency, as well as excite the respiratory center, have pronounced hepatoprotective properties [41, 53].

Rhaponticum carthamoides (Willd) DS, which, due to the content of lignans, is characterized by a general tonic and stimulating effect of the central nervous system, and due to the presence of ecdysteroids, the anabolic activity is characteristic of it. Preparations of *Rhaponticum carthamoides* (Willd) DS are recommended not only for patients, but also for healthy people with asthenia, a reduced efficiency and a reduced speed of protein-synthesizing processes, as well as for people whose professional activity requires increased physical endurance. There are obvious prospects for the development of MPs and BAFAs for sports medicine, especially for those kinds of sports where a rapid adaptation to the physical exertion, an acceleration of protein metabolism, and a rapid gain of muscle mass are required [43–45].

Melissa officinalis L. serves as a source of drugs with an opposite effect on the central nervous system – anxiolytic and, to a lesser extent, a sedative effect. However, in terms of immunomodulatory and antioxidant effects, the plant is apparently underestimated. A wide range of activities of the raw materials and preparations of *Melissa officinalis* L. is realized due to the diverse chemical composition: caffeic acid and neolignan based on it – rosemary acid – cause immunomodulatory and antioxidant effects, as well as an anxiolytic one; the essential oil, the main components of which

DOI: 10.19163/2307-9266-2023-11-5-399-411

are citral, citronellal, linalool, geraniol, nerol, etc., is mainly responsible for sedative and antispasmodic effects [46, 47].

Thus, the uniqueness profile of biological and pharmacological activities of the phenylpropanoid class makes it possible to consider the MPRMs of the corresponding plants as promising MPRMs for obtaining organoprotectors relevant for medical and preventive purposes, effectively acting not only on the main pathogenetic links in the development of the disease, but also, importantly, through the mechanisms of sanogenesis triggering the activation of their own protective body systems.

CONCLUSION

The analysis of the scientific literature has shown a high level of knowledge about phenylpropanoids, considered as an independent class of natural compounds, in terms of the features of their chemical structure, biosynthesis, classification, distribution in the world of plants, and use in medical practice.

The characteristic profile of the biomedical properties of the phenylpropanoids class has been described – the expediency of considering them as organoprotectors. Their effect on the body realized through mechanisms of the antioxidant protection, maintenance of specific and nonspecific resistance of the organism, a homeostasis system, including the conditions of the increased mental and physical exertion, has been shown.

The most characteristic types of specific pharmacological activity include: hepatoprotective, immunomodulatory, tonic (for derivatives of cinnamon alcohols) action; the advantages of using a native complex of compounds in the development of medicines are shown.

Based on the analysis of the literature data and the published experimental materials of the authors' own,, the review formulates prerequisites for the further development of MPs and BAFAs based on the MPRMs containing phenylpropanoids from the standpoint of the relationship of "chemical structure – pharmacological action – application".

FUNDING

This study didn't receive any support from outside organizations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

All the authors confirm that their authorship meets the ICMJE international criteria (all the authors contributed substantially to the conceptualization, research and preparation of the article, read and approved of the final version before publication). Vladimir A. Kurkin – methodology and scientific guidance for compiling the review, systematization of data from the global publication flow, writing and editing the manuscript; Natalia R. Varina – search for scientific literature, selection and critical analysis of the material, its presentation, writing the manuscript; Elena V. Avdeeva – responsible for the concept of the review and a block of data on preparative study, biological and pharmacological activity of phenylpropanoids, the compiler of these sections, writing the text of the manuscript; Irina V. Ruzaeva – writing a section on the distribution of phenylpropanoids in the plant world.

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