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Review Article

# A Holistic Approach to the Development of Multi-Targeted Medicines (Using the Example of the Phenylpropanoid Class)

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## Abstract

The article is devoted to the use of a holistic approach for targeted drug development based on the etiopathogenesis of conditions and diseases. The implementation of the approach is discussed using the example of a currently actively studied class of biologically active substances, phenylpropanoids, as having a polytargeting effect. At the same time, the relevance of developing the methodological foundations of a special section of pharmacology - phytopharmacology and the request of practical healthcare for organoprotective drugs is taken into account.

The aim of the study was to substantiate the feasibility of using a holistic approach in the creation of polytargeted medicines and to develop a design for their preclinical and clinical study based on the etiopathogenesis of conditions.

**Discussion:** The published data show that from the standpoint of evidence-based pharmacy, it is important to have an in-depth knowledge of the chemical composition of raw materials and drug candidate substances; on this basis, to obtain standardized pharmacologically active substances; further, to study their safety and effectiveness for the body as a whole. Thus, for a targeted study of the effects of phenylpropanoids on the nodal links of pathogenesis (and sanogenesis), a corresponding fragment of cause-and-effect relationships in disorders of specific and nonspecific body resistance was constructed. The presented etiopathogenesis architecture

determined the content of the conducted preclinical and clinical study of phenylpropanoids and their derivatives. On this basis, and taking into account the data of other researchers, the corresponding architecture of phenylpropanoid pharmacodynamics has been developed. The information that is constantly being updated in the publication data set confirms the correctness of the architectures, which does not exclude their subsequent completion.

**Conclusion:** When developing drugs, especially if a targeted effect is predicted, it is advisable to base the design of preclinical studies on the architecture of etiopathogenesis, ideally using etiopathogenetic experimental models at different levels of the organization of the living. Then it should be expected that further clinical application will implement the principle: we treat not the disease, but the patient, and taking into account the introduction of artificial intelligence technologies, a complete personification of pharmacocorrection will be achievable.

**Keywords:** Holism; Holistic Model of Health; Architecture of Etiopathogenesis; Polypharmacology; Phenylpropanoids; Organoprotection

## Abbreviations

BAC: Biologically Active Compounds; WHO: World Health Organization; CNS: Central Nervous System; ROS: Reactive Oxygen Species; LPO: Lipid Peroxidation Process; ICC: Immunocompetent Cell; SOD: Superoxide Dismutase

## Introduction

The concepts of "holism" and "holistic" come from the Greek word "holon" (ὅλος - "whole, integral, integrity"), and in a broad sense is a position in philosophy and science on the problem of the correlation of part and whole, proceeding from the qualitative uniqueness and priority of the whole in relation to its parts [1]. The algorithm for the integrity of an organism was formulated by the ancient Greek scientist Heraclitus in the 5th century BC: "From one, everything, from everything is one," and then Aristotle in the 4th century BC developed this idea in his writings: "The whole is something besides the parts" [2]. The well-known principle is the same: "It is not the disease that needs to be treated, but the patient," proclaimed back in the 5th - 4th century BC by Hippocrates. That is, the disease is part of the whole, and the whole is an organism with all its internal and external causal relationships of both physical and non–physical nature, and developing over time [3].

For a long time, until the middle of the 17th century, holism as an approach to understanding the world and man in it was considered the only true one. Holistic medicine (integral or naturopathic, understood now as an alternative) was actively developing, treating not organs, but the entire system, body and soul as a whole. But further, with the development of sciences, including natural sciences and, in particular, medicine (now designated as traditional), holism faded into the background, remaining to this day one of the philosophical concepts [4].

Mass interest in the ideas of holism was revived in the 20th century. And this is a great merit of the South African philosopher and politician Jan Christiaan Smuts, who in 1926 introduced the term "holism" into the philosophical conceptual apparatus and outlined the key provisions of the "philosophy of integrity". However, Russian outstanding clinicians of the 19th century, primarily M.Ya. Mudrov (1776-1831) and S.P. Botkin (1832-1889), followed the principle: "Treat not the disease, but the patient" and promoted the approach of the "father of medicine" Hippocrates [5].

Considering that until the twentieth century there was no modern understanding of the etiology and pathogenesis of diseases, as well as modern methods of diagnosis and treatment, it is amazing how, based on empirical data and clinical observations, ancient thinkers and Russian medical scientists at the philosophical level saw the essence of things - a system of cause-and-effect relationships for each patient, methodologically correct they interpreted the interaction of the concepts of "illness" and "sick", taught: "it is necessary to start treatment from the root, that is, from the causes".

In this regard, we should also pay tribute to the historically established medical systems and practices of different peoples of the world, which today have reached a new level of evidence and achievements, for example, traditional medicine in India, China and other countries [6,7]. Their contribution to the formation of individual areas of practical healthcare in the concept of holistic medicine (when the body is understood as a whole) is also obvious for European medicine - these are acupuncture, osteopathy, homeopathy, phytotherapy, etc.

To date, a request has been formed to develop the methodological foundations of such a section of pharmacology (more precisely, polypharmacology), as a phytopharmacology, and for the targeted development of herbal medicines with proven effectiveness [8]. We especially note the controversial understanding of organoprotective drugs (note that organoprotection is a well-known approach in pharmacotherapy) - from the conceptual framework to the justification of their use for therapeutic and preventive purposes. A number of answers can be found using a holistic approach, especially since the amount of accumulated and published data allows us to approach from the standpoint of evidence-based medicine to a deep understanding of the cause-and-effect relationships that form pathological conditions and clusters of associated diseases [9].

The aim of the study was to substantiate the feasibility of using a holistic approach in the creation of polytargeted medicines and to develop a design for their preclinical and clinical study based on the etiopathogenesis of conditions.

## Materials and Methods

The main method used in the article was the analysis of the following databases: databases on signal transduction pathways - Pathway Interaction Database (PID), Reactome, about metabolic pathways - BRENDA, KEGG, scientific articles in the eLibrary.ru, Scopus, PubMed, PubChem, Cyberleninka. 67 articles were selected as the most significant out of more than 1,500 analyzed by the subject of the review.

## Results and Discussion

The holistic model of health considers all aspects of the human body in their interrelation and interdependence [10]. In a broader sense, it is a holistic consideration of the somatic, psychophysical, mental, social and spiritual well—being of a person.

Accordingly, the following health components are distinguished:

- Somatic component (genotype, metabolic rate, level of physical development, type of constitution, functional state and reserve capabilities of organs and body systems of the "holistic patient").
- Psychological component (emotional, volitional and intellectual spheres of personality, hemisphere dominance, temperament, etc. aspects of "holistic psychology").
- Socio-spiritual component (goals, moral values, ideals, actual needs, level of aspirations, degree of recognition, understanding of the body-soul relationship). These aspects, in particular, are included in the concept of "mental health group" (according to Grombakh SM).

It is important that the Constitution of the World Health Organization (WHO, Geneva, 1968) defines health not only as the absence of (somatic) diseases, but as a state of complete physical, mental and social well-being, which fully correlates with a holistic approach. At the same time, today in traditional medicine, even in preventive medicine, differentiation dominates integration or integrity more than in other fields of science [11]. In terms of expanding the scope and deepening knowledge about the body, this is natural and correct, but it should not be opposed to a holistic approach: the disease model and the health model are both holistic. It is more correct to consider the mutual development of models in a spiral and in the transition from quantity to quality – it is necessary to bring the understanding of integrity to a new level [12]. Today, when a huge amount of medical data has been accumulated and computing power is actively developing, the links of etiopathogenesis of a wide nosological spectrum of diseases have been studied in sufficient depth, and at different levels of the organization of life, it is necessary to systematically and evidence-based return to the ideas

of a holistic understanding of health and disease [13], including going deeper into the development of drugs at the level of pharmacogenetics [14].

The prospects of using a holistic approach for the targeted development of medicines (drugs) today, in our opinion, can be represented by several successive components:

- Building clusters of etiopathogenesis of conditions and diseases as a roadmap for studying the mechanisms of action and the spectrum of pharmacological activity of active substances/BAC;
- The study of drugs at the preclinical stage, starting with virtual screening and further along the levels of organization of the living, and subsequently at the clinical stage with the maximum possible coverage of cause-and-effect relationships in the formation of pathology and associated diseases;
- Pharmacocorrection is aimed not only at eliminating individual symptoms, but also at a complex of factors affecting a person, as well as all the components that form health (holistic health model);
- In the treatment of chronic diseases, as well as their primary and secondary prevention, it is advisable to influence both the interrelated links of pathogenesis (a multi-targeted approach) and the opposite links of sanogenesis (organoprotection) [15].

In this regard, herbal medicines are the most promising and safe when used correctly [16]. At the same time, while there is relative clarity in understanding the design of the study with synthetic molecules, starting with *in silico* models and subsequent interpretation of the results of pharmacological studies [17], in the case of herbal medicines, everything is much more complicated due to the multicomponence of BAC contained in phytopreparations and the breadth of action on the body [18].

## Focusing the action of medicines

When creating and using therapeutic drugs, there are several general methodological approaches in terms of focusing the effects of active substances / BAC. The first approach is based on the targeted effect of active substances, which achieves high efficiency, specificity and, accordingly, is expected to have no effect on other processes (safety) [19]. The second approach, on the contrary, assumes a combined effect on a number of processes – the synergetic coverage of clusters of etiopathogenesis and sanogenesis (and their corresponding derivatives - diseases and their clusters), where organoprotective action, synergistic positive effects (antioxidant, anti-inflammatory, antiseptic, etc.) may be an advantage [20]. Of course, there are different combinations of approaches and methodologies aimed at blocking the links of pathogenesis and/or activating and modulating the links of sanogenesis [21].

Common in the implementation of these approaches is the effect of active substances on body conditions, and the disappearance of symptoms and normalization of homeostasis parameters, reflected in a number of medical indicators (and other medical data), is a logical consequence of eliminating the actual pathological processes. At the same time, the implementation of point effects covers research in the field of molecular targets, the study of protein-protein interaction, the creation of specific molecules – blockers, inhibitors, activators of kinases and other enzymes, cytokines, neurotransmitters, hormones and other substrates, as well as pharmacogenetics [22]. The organoprotective approach is associated with the realization of receptive and postreceptive effects (sometimes synergetic) on different links of pathogenesis and sanogenesis at different levels of the organization of living organisms and is more inherent in multidirectional molecules or combinations of active substances [23]. As a rule, the first approach is used by the creators of drugs that include one type of molecule, although organoprotection is observed in individual molecules with a polytargeted effect or distribution of receptors across a number of locations in the body. But with almost no exceptions, the second approach (complex, multitargeted) is applicable for extraction preparations from medicinal plant raw materials and other multicomponent preparations. The use of the term “polypharmacology” is correct for them [24]. There is a subtle point here, since the toxic properties of drugs potentially result from the non-selectivity of exposure and binding of non-organotropic structures. To avoid this, it is necessary to develop predictive algorithms for a comprehensive assessment of the effect, in particular, of organoprotectors on the body (which will be further demonstrated by the example of a separate class of BAC).

Accordingly, in the first direction, scientists’ attention is focused on identifying therapeutically significant targets for drug exposure, predicting interactions using various virtual screening methods, subsequent synthesis of molecules, and studying them experimentally, and in the second direction, studying various effects at the tissue or body level, usually exerted by complexes of active substances [25].

Of course, at the present stage, both in the case of a targeted and a multi–targeted approach, all three key positions should be achieved: "chemical structure – mechanism of action - pharmacological activity/effect" [26]. For this purpose, it is important to develop progressive models that reproduce the etiopathogenetic situation, especially *in vivo* models for studying pharmacodynamics. This is achieved, for example, by creating toxic damage of an iatrogenic nature (the toxic effect of drugs – paracetamol, indomethacin, etc.) or by using compounds formed along a chain of signaling pathways that trigger links in the pathogenesis of the studied diseases and their clusters. This type of experimental models, etiopathogenetic (holistic) models of the disease, are interesting both for studying pathology as such and for studying the pathogenetic effects of the drugs under study.

## Polytargeting BAC and phytopharmacology (using phenylpropanoids as an example)

When talking about examples of poly-targeted/multi-targeted medicines, it is necessary to refer to herbal medicines, most of which have a favorable toxicity profile [27]. And it should be noted that the multicomponent composition, the assignment of compounds to several classes of natural BAS, brings medicinal herbal preparations (not only medicinal herbal preparations, but also extraction preparations, individual substances) into a separate subject field – into a special section of pharmacology called phytopharmacology [28,29].

The source of polytargeted drugs includes medicinal plants containing phenylpropanoids and their derivatives as the dominant group of active compounds (compounds of a predominantly aromatic nature based on the phenylpropane fragment $C_6$-$C_3$). This class of BAC has also been found in fungi and bacteria, which have been used in recent years to produce these compounds through metabolic synthesis [30].

Simple phenylpropanoids (based on a single phenylpropane fragment) are the biogenetic precursors of a large number of other compounds of a phenolic nature, which in turn have pharmacological activity [31]. The spectrum of activity of phenylpropanoids and their derivatives can be characterized as organoprotective, which allows us to consider a holistic approach to the creation of drugs using the example of this class of BAC.

In this regard, the issues of studying the chemical composition and chemical standardization of phytopreparations in order to obtain reliable data and interpret the results, starting with methods for predicting activity *in silico* and determining the class of toxicity in experiment, are relevant and basic for subsequent discussion of pharmacological activity and indications for the use of drugs [32].

As a result of the analysis of scientific literature data on more than 15 types of medicinal plants containing phenylpropanoids and their derivatives, the main significant substances that should be considered as analytes in the identification and determination of the appropriate quality of medicinal plant raw materials and as target substances in the preparation of medicinal products were found [33]. The individual representatives of phenylpropanoids, divided into groups, were shown in Table 1.

Among simple phenylpropanoids, glycosides of cinnamic alcohols and derivatives of cinnamic acids are of the greatest interest in terms of biological and pharmacological activity: cinnamylglycosides (glycosides of cinnamic alcohol) of *Rhodiola species*, conjugates based on caffeic acid of *Echinacea purpurea* (L.) Moench., phenylpropanoid glycosides based on synaptic alcohol of *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., *Syringa vulgaris* L. and many other compounds [34-36].

With regard to complex phenylpropanoids (lignans), it should be noted that their diversity is due to the oxidative combination of $C_3$-fragments, as well as other structural units included in their molecule. The most numerous subgroup are phenylethanoid derivatives (complex phenylpropanoids – acteoside, forsithiazide, echinacoside, plantamaioside) [31].

A deep study of the structure of compounds and the spectrum of activity of phenylpropanoids has led to the search and discovery of ways to obtain them by chemical, enzymatic and microbiological synthesis. In particular, more attention is being paid to the use of genetically modified microbial cells for the production of valuable rosmarinic acid, which has high antioxidant, antimicrobial, immunostimulating, antiviral, and antitumor activity [37,38].

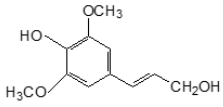
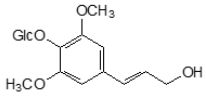
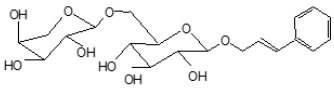
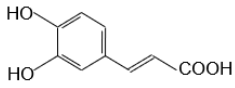
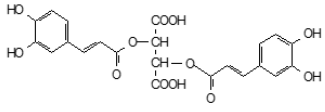
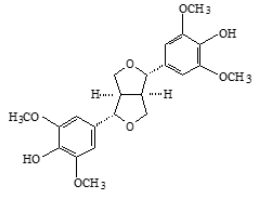
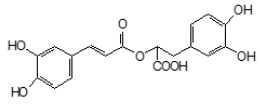
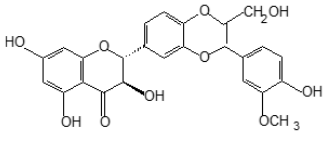
| Group of phenylpropanoids, representatives | Plant source |
|---|---|
| Simple phenylpropanoids | |
| *Cinnamon alcohols and their glycosides - cinnamylglycosides*<br>  <br>Synaptic alcohol<br>  <br>Syringin (eleutheroside B)<br>  <br>Rosavin | *Eleutherococcus senticosus* (Rupr. et Maxim.) *Maxim. (*family *Araliaceae), Syringa vulgaris* L. (family *Oleaceae*), *Rhodiola species* (family *Crassulaceae*), *Salix viminalis* L. (family *Salicaceae*) |
| *Hydroxycinnamic acids and their derivatives*<br>  <br>Caffeic acid<br>  <br>Chicoric acid | *Echinacea purpurea* (L.) Moench (family *Asteraceae*) |
| Complex phenylpropanoids | |
| *Lignans*<br>  <br>Syringoresinol | *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (family *Araliaceae*) |
| *Neolignans*<br>  <br>Rosmarinic acid | *Melissa officinalis* L. (family *Lamiaceae)* |
| *Flavolignans*<br>  <br>Silybin | *Silybum marianum* (L.) Gaertn. (family *Asteraceae)* |

**Table 1:** The structural diversity of the phenylpropanoid class and their plant sources.

The mentioned plants and a number of other plant sources have been the subject of many years of research by SamSMU scientists studying both the chemical composition and the spectrum of biological and pharmacological activity of individual compounds and drugs being developed. The structures and physical-chemical properties of phenylpropanoids have been established and studied, and some of the compounds have been given the status of state standard samples (rosavin, syringin, triandrin, silybin, etc.) [39]. The issues of chemical standardization of the studied types of medicinal plant raw materials have been solved using modern instrumental analysis methods, which is reflected in the 13th and 15th editions of the State Pharmacopoeia of the Russian Federation, as well as in the harmonization of methods of qualitative and quantitative analysis of BAC in the series: medicinal plant raw materials – active pharmaceutical substance – medicinal product [40].

Further from understanding: What influences? - we can move on to the question: What does it affect?

## Holistic approach in building the target architecture of etiopathogenesis

Based on our own data and the work of other Russian and foreign scientists in the field of pathophysiology, pathobiochemistry and pharmacology [41], from the perspective of using a holistic model, we modeled a fragment of the architecture of some interrelated pathological processes under the influence of damaging factors of an infectious and non-infectious nature (Figure 1). The architecture of etiopathogenesis (fragment), reflected in the enlarged plan, includes links of pathogenesis in their interrelation, in relation to which it is advisable to consider the sphere of influence of the studied class of BAS today [31,42]. These include: changes in the homeostasis system, including immune homeostasis, oxidative stress as a common link in the pathogenesis of a number of pathological conditions, disorders in higher regulatory activity on the part of the central nervous system. Specific links of pathogenesis are highlighted with the symbol "•" on the diagram, which served as a focus for studying the mechanisms of action in the design of preclinical and clinical studies.

## Holistic approach in building the architecture of pharmacody-

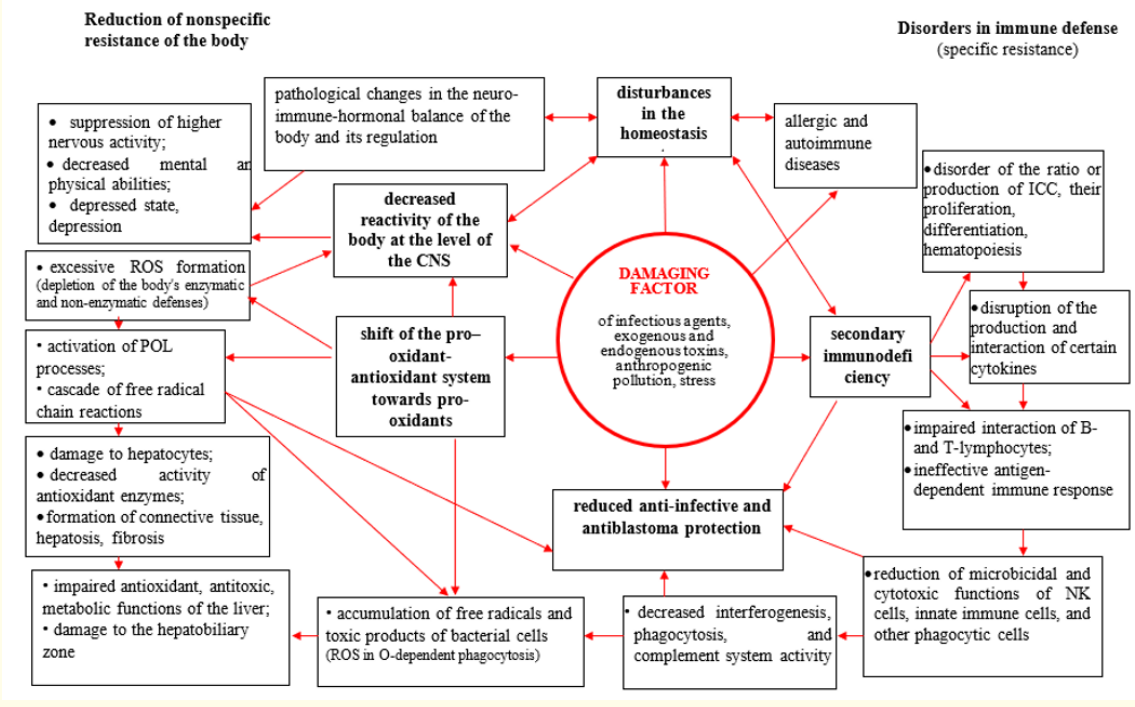



**Figure 1:** The effect of "damaging factors" on some links of the nonspecific and specific resistance of the body ("•" - pathogenetic links are indicated).

## namics

Analyzing the global publication flow, the volume of which is impressive, it should be noted the breadth of researchers' coverage of the types of activity of the phenylpropanoid class in experimental studies. In particular, numerous data obtained *in vivo* on models of poisoning mainly with carbon tetrachloride and the formation of toxic hepatitis are presented.; effects on the cellular and humoral link of immunity, on the cytokine profile, on the behavior of animals in the "despair" test, the "punishable behavior" test, the "forced swimming" test, experimental reactions in the "open field" installation; antihypnogenic effects and a number of others. Antioxidant activity has also been studied in *in vitro* model systems, and a correlation with hepatoprotective activity has been noted, including *in vivo* [43,44].

The study of the mechanisms of action (neurotropic, adaptogenic, antioxidant, hepatoprotective, immunomodulatory, and a number of others) was carried out both in relation to individual compounds and their mixtures, as well as drugs. As a result, certain relationships have been identified in the series: "chemical structure – pharmacological effect" in relation to a number of pathological conditions and the range of indications for the use of drugs based on phenylpropanoids for preventive purposes has been substantiated [45].

For example, it has been established that derivatives of cinnamon alcohols have a wide range of neurotropic activity - tonic, nootropic, antihypnogenic, whereas derivatives of cinnamon acids do not have such activity, which is described in more detail in a number of dissertation studies, patents and scientific articles. The antioxidant activity increases with an increase in the number of -OH и -$OCH_3$ groups, as well as the appearance of a lactone group in the structure of flavolignans (moreover, dehydrosilybin turned out to be more active than silybin) [43,46].

As a result of the systematization of published information, based on and by analogy with the architecture of etiopathogenesis (Figure 1), the architecture of pharmacodynamics for the class of phenylpropanoids was counter-constructed (Figure 2). That is, the answer to the following question regarding the class of phenylpropanoids is systemic presented: how are they affected, what is the spectrum of pharmacological activity? In this diagram, the identified links of influence on pathogenesis and activation or modulation of sanogenesis links are also marked with the symbol: "•". The arrows show causal relationships, which, in our opinion, can be a guideline for creating etiopathogenetic experimental models. In a simpler version, these relationships can be used to select combinations of already known models to cover the design of the study of interrelated states at different levels of the organization of life and to obtain numerical characteristics of the analyzed parameters (homeostasis, lipid spectrum, biochemical parameters, etc.).

The practical way out of using the etiopathogenetic approach

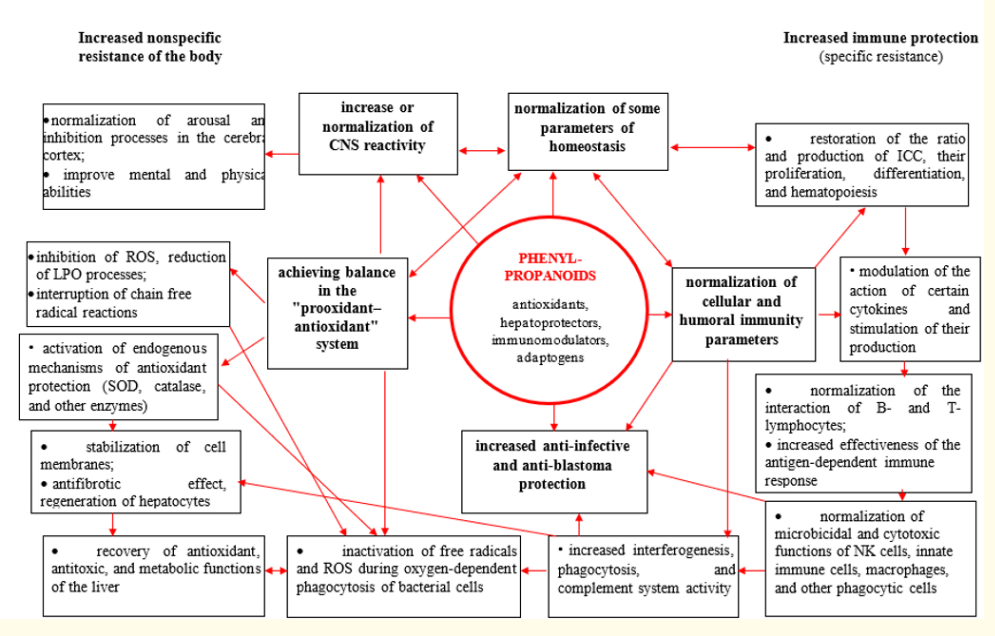



**Figure 2:** The effect of phenylpropanoids on some links of nonspecific and specific resistance of the body ("•" indicates the main components of pharmacological effects – links of sanogenesis).

in the creation of extraction preparations based on phenylpropanoids, for example, is the development of SamSMU - tincture of *Rhodiola rosea*, tincture of *Echinacea purpurea*, liquid extract of *Silybum marian*um, tincture of *Melissa officinalis*, complex preparations "Silibochol", "Dentos" and others. Their use in clinical practice, as well as a large number of drugs created independently or in collaboration with Samara scientists, fully justified the appointment of phenylpropanoids as tonic, antioxidant, immunomodulatory, hepato-, nephro- and cardio-protective agents. Moreover, it is advisable to prescribe them both for therapeutic purposes and as a means of primary and/or secondary prevention [44].

Taking into account the classification of phenylpropanoids as low-toxic compounds, this class of BAS can be confidently considered in terms of the breadth of effects on various links of specific and non-specific resistance, influence on higher regulatory systems, and on the homeostasis system as organoprotectors [44,46].

Taking into account that data on both etiopathogenesis and pharmacological properties, for example, rosmarinic acid and syringin (eleutheroside B), are constantly being updated (and so far fit correctly into the presented architectures), it should be expected that the discussed architectures may expand and reveal new cause-and-effect relationships [41,47]. And, almost certainly, it will be supplemented and specified taking into account the increasing immersion of researchers in the study of genetically determined states, the discovery of molecular mechanisms in the development of pathological processes, and the use of mathematical modeling, for example, protein-protein interaction [48].

This shows the commonality of targeted and multi-targeted approaches based on etiopathogenesis, which makes pharmacology, including polypharmacology, an increasingly evidence-based subject area. Further prospects for using the holistic approach are seen in assessing the weights of the significance of pathological processes in the formation of pathological conditions and the occurrence of associated diseases based on meta-data [49]. And on this basis, with the development of computational pharmacodynamics and the introduction of AI technologies into drug design, pharmacology (and, in particular, phytopharmacology) will reach the level of systemic pharmacology, considering the action of drugs as the result of a network of interactions and effects caused by them [50]. In our opinion, this should be considered the pinnacle of the modern embodiment of a holistic approach in the development and application of medicines.

## Conclusion

An objective understanding of the chemical composition and properties of active substances (structure, physico-chemical characteristics, spectrum of biological and pharmacological activity, safety) is fundamentally important at the stage of preclinical and clinical study of medicines, in particular, with a multi-targeted nature of action.

An appropriate approach to the study in the experiment and at subsequent stages of clinical trials is the use of a holistic approach, in particular, implemented in building the architecture of etiopathogenesis of conditions and diseases in accordance with the intended direction of action of the drug being created.

The presented fragment is the architecture of etiopathogenesis, formed under the influence of damaging factors on the links of non-specific and specific body's defenses, which served as the basis for the design of preclinical and clinical studies of the class of phenylpropanoids, for which the corresponding pharmacodynamic architecture has been formed and the organoprotective effect on the body has been proven.

The proposed approach develops the methodological aspects of phytopharmacology and implements the principle: we treat not the disease, but the patient.

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