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MEDICINE AND PHARMACY

Prospects of Pharmacological Study of Potential Medicinal Products Containing Biologically Active Substances of Natural Origin for the Treatment of Skin Diseases

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Abstract. Skin diseases remain an urgent medical and social problem due to their significant prevalence, tendency to chronic and recurrent course, diversity of pathogenetic mechanisms and the need for long-term pharmacotherapy. A promising direction of modern experimental and clinical pharmacology is the study of biologically active substances of natural origin as a potential basis for the creation of drugs with anti-inflammatory, antioxidant, antimicrobial, immunomodulatory and reparative properties. Given this, the purpose of this work - to summarize current scientific data on the pharmacological activity of biologically active substances of natural origin, to characterize the molecular mechanisms of their action, and to identify promising areas of experimental study of potential drugs for the treatment of skin diseases. To achieve the goal , a narrative analysis of modern scientific publications devoted to the pharmacological properties of natural biologically active compounds, the mechanisms of their influence on inflammation, oxidative stress, tissue regeneration, and the functional state of the epidermal barrier was conducted. It has been established that the greatest pharmacological interest is represented by polyphenolic compounds, flavonoids, terpenoids, saponins, alkaloids, polysaccharides and other natural metabolites that can influence key links in the pathogenesis of dermatological diseases. The prospects of these substances are associated with the modulation of the NF-κB, MAPK, Nrf2/ARE signaling pathways, regulation of the expression of pro-inflammatory cytokines, reduction of the

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intensity of free radical processes and maintenance of reparative mechanisms. At the same time, the degree of clinical evidence for different natural compounds differs significantly . Therefore, biologically active substances of natural origin constitute a promising group of compounds for the development of new dermatological drugs. Further studies should be aimed at establishing the relationship between chemical structure and pharmacological activity, standardization of composition, determination of efficacy and safety, as well as optimization of dosage forms for topical use.
Keywords: *biologically active substances, natural compounds, pharmacological activity, skin diseases, flavonoids, polyphenols, oxidative stress, anti-inflammatory effect, repair, dermatopharmacology.*

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Modern dermatology is characterized by a growing interest in the search for new pharmacological approaches aimed at the comprehensive correction of pathogenetic mechanisms of skin diseases. Of particular importance are chronic inflammatory dermatoses, in particular atopic dermatitis, psoriasis, acne, contact dermatitis, as well as disorders of reparative processes, which are accompanied by prolonged inflammation, oxidative stress and structural and functional changes in the skin barrier.

Despite the significant arsenal of modern drugs, some aspects of pharmacotherapy of dermatological diseases remain insufficiently resolved. In particular, long-term use of certain drugs may be limited by the development of adverse reactions, insufficient effectiveness in certain categories of patients, the need for individualization of treatment, and the risk of recurrence of the pathological process.

In this context, natural biologically active substances, which are characterized by significant structural diversity and a wide spectrum of potential pharmacological activity, deserve special attention [1, 2, 3, 4].

The results of modern research indicate that natural compounds can modulate intracellular signaling mechanisms, regulate the production of inflammatory mediators, influence the processes of keratinocyte proliferation and differentiation, fibroblast activity, synthesis of extracellular matrix components, and restoration of epidermal barrier integrity [5-8, 9, 10] .

At the same time, the natural origin of a substance is not a guarantee of its safety or clinical efficacy. Therefore, the creation of medicines based on natural components requires systematic pharmacological research using modern experimental models and methods for assessing biological activity [5, 7, 10].

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The purpose of the study is to conduct a comprehensive analysis of the pharmacological properties of biologically active substances of natural origin, to determine the main molecular and cellular mechanisms of their influence on pathogenetic processes in skin diseases, and to substantiate promising directions for the creation of new dermatological drugs.

Materials and methods . The work was carried out in the format of a narrative review of scientific literature using publications presented in the international scientific information resources PubMed and open scientific publications. The main attention is paid to studies of the pharmacological activity of natural compounds, their molecular targets, effects on inflammation, oxidative stress, proliferation and regeneration of skin cells. The analysis included experimental studies in vitro, in vivo, review publications and available clinical data. The results were evaluated taking into account the type of study, biological model and the possibility of transferring the results to clinical practice.

Results and discussion . Natural biologically active substances are a chemically heterogeneous group of compounds that can affect different links in pathological processes in the skin. Of particular interest are polyphenols, flavonoids, terpenoids, triterpene saponins, alkaloids, and polysaccharides. Their potential pharmacological value is determined not only by individual biological effects, but also by the possibility of simultaneous influence on several interrelated pathogenetic mechanisms (Table 1) [5-8, 9, 10].

Table 1

Main groups of biologically active substances of natural origin and their potential pharmacological effects in skin diseases

Group of compounds	Representatives	Main effects studied
Flavonoids	Quercetin, luteolin, apigenin	Anti-inflammatory, antioxidant
Polyphenols	Resveratrol, catechins	Antioxidant, cytoprotective
Terpenoids	Asiaticoside, madecassoside	Reparative, anti-inflammatory
Alkaloids	Berberine	Anti-inflammatory, antimicrobial
Polysaccharides	Acemannan, β-glucans	Immunomodulatory, reparative
Phenolic acids	Coffee, ferulic	Antioxidant, photoprotective

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Thus, biologically active substances of natural origin are characterized by a variety of pharmacological effects, among which anti-inflammatory, antioxidant and cytoprotective activity are of leading importance [6, 7, 8, 9, 11]. The above properties mainly characterize experimentally established effects, rather than confirmed clinical indications for each substance.

Of particular scientific interest is the study of molecular mechanisms of pharmacological effects of biologically active substances of natural origin. Modern experimental studies indicate their ability to influence key signaling pathways involved in the development of inflammation, oxidative stress and disruption of the functional state of the skin barrier. The main mechanisms of anti-inflammatory and antioxidant action of natural compounds, in particular flavonoids, are summarized in Figure 1 [6, 8, 11] .

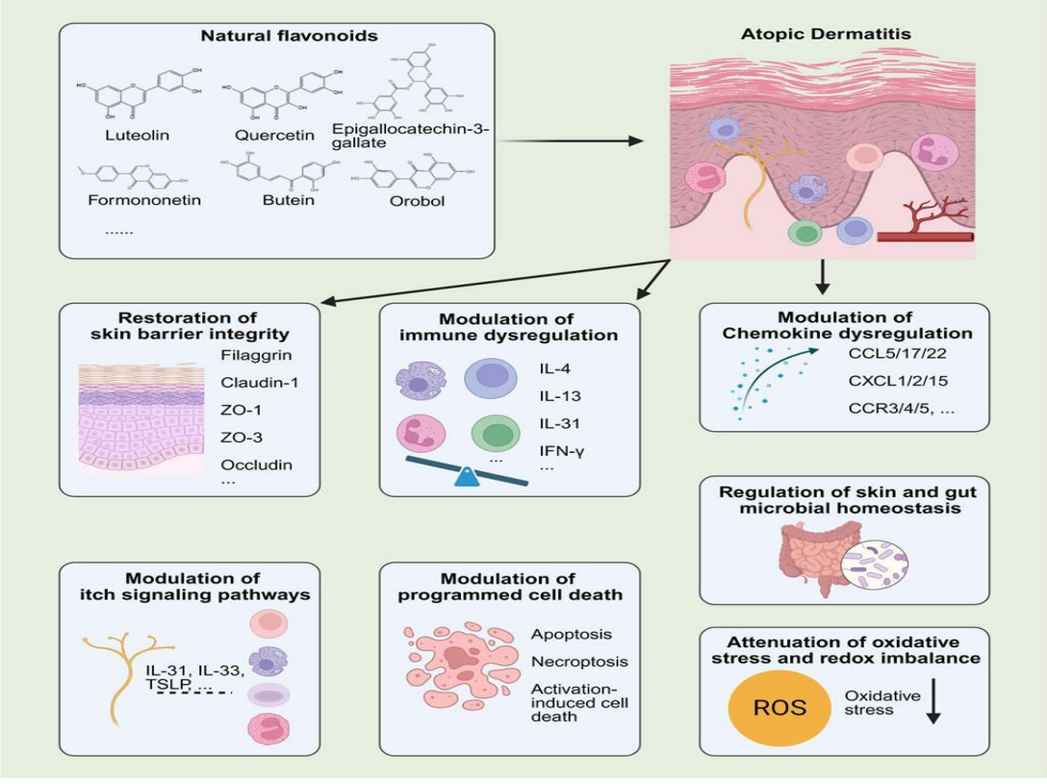


Fig. 1

Molecular mechanisms of anti-inflammatory and antioxidant effects of natural biologically active substances in inflammatory skin diseases [8].

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Thus, the influence of natural biologically active substances on key molecular mechanisms of inflammation and oxidative stress justifies the prospect of their further pharmacological study for the development of new dermatological drugs.

One of the leading mechanisms of the development of most inflammatory skin diseases is dysregulation of the local immune response, which is accompanied by excessive production of pro-inflammatory cytokines, activation of immunocompetent cells, and disruption of intercellular interaction. Tumor necrosis factor α (TNF-α), interleukins IL-1β, IL-6, IL-17, IL-23, and other mediators play an important role in these processes, the significance of which depends on the specific disease. Experimental studies indicate that a number of natural polyphenolic compounds are able to inhibit the activation of the nuclear transcription factor NF-κB, affect MAPK-dependent signaling cascades, and reduce the expression of certain pro-inflammatory mediators.

In particular, quercetin has been shown to modulate the production of TNF-α, IL-1β, IL-6, as well as the activity of cyclooxygenase-2 and inducible NO synthase in experimental models [6, 8] . From a pharmacological point of view, these effects justify further study of natural compounds as potential components of topical anti-inflammatory drugs.

Oxidative stress is one of the important mechanisms of cellular damage in inflammatory, metabolic, and reparative skin disorders. Excessive formation of reactive oxygen species causes oxidative modification of lipids, proteins, and nucleic acids, disrupts the functioning of cell membranes, and maintains a chronic inflammatory response.

Polyphenolic compounds can exert antioxidant effects through direct interaction with free radicals, chelation of metal ions, and regulation of endogenous antioxidant systems [6, 7, 11] . Of particular importance is the Nrf2/ARE signaling pathway, which is involved in the regulation of the expression of cytoprotective and antioxidant enzymes.

Promising experimental indicators of pharmacological activity of natural compounds include levels of malondialdehyde, reduced glutathione, superoxide dismutase, catalase, and glutathione peroxidase activities.

It has been determined that the assessment of antioxidant activity should be considered as a component of a comprehensive pharmacological study of potential dermatological drugs. The processes of repairing damaged

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tissues include sequential and interconnected stages of hemostasis, inflammation, proliferation, and remodeling of the extracellular matrix. Dysregulation of these processes can lead to delayed epithelialization, the formation of chronic wounds, and pathological scarring. In experimental studies, certain natural substances have demonstrated the ability to influence keratinocyte migration, fibroblast proliferative activity, collagen synthesis, and angiogenesis processes. Of particular interest are the triterpene compounds of Centella asiatica, in particular asiaticoside and madecassoside, which are being investigated for their potential effects on reparative mechanisms [5, 7, 10] .

For a deeper understanding of the pharmacological potential of natural biologically active substances, it is advisable to consider the molecular mechanisms of their influence on inflammatory processes and oxidative stress in skin tissues. The main signaling pathways through which these effects are realized are schematically presented in Figure 2.

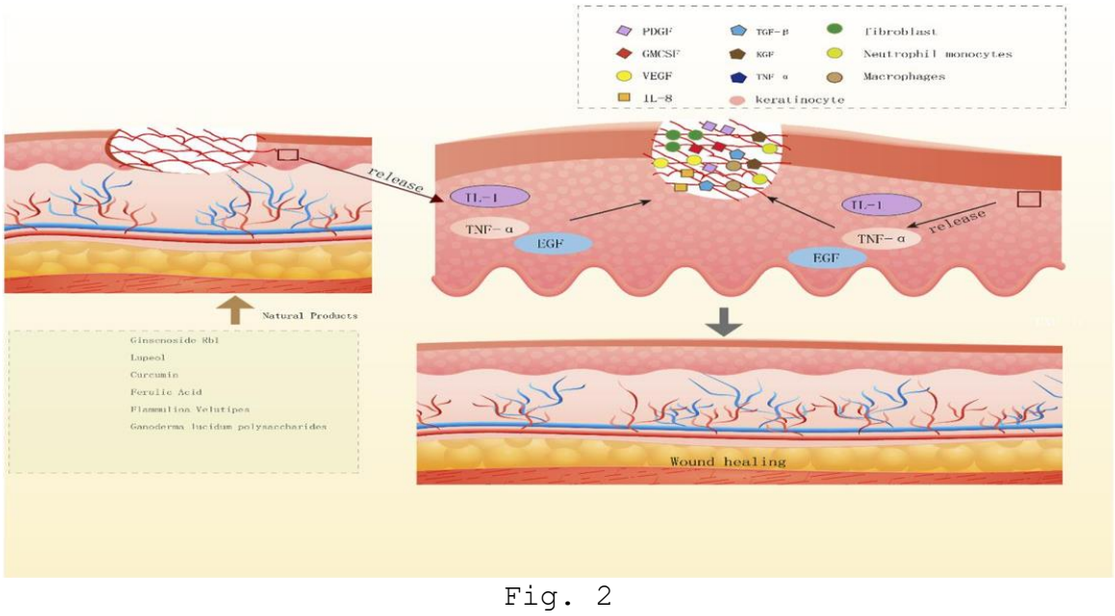


Fig. 2

Potential mechanisms of influence of biologically active substances of natural origin on angiogenesis in the process of skin repair [10].

Molecular targets may include TGF-β/Smad signaling systems, VEGF, and other regulators of cell proliferation and tissue remodeling.

Disruption of the skin microbiota composition and excessive colonization by certain microorganisms can maintain

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inflammation and worsen the course of dermatological diseases. In this aspect, natural compounds with potential antibacterial and antifungal activity are of pharmacological interest. Their effects may be associated with disruption of the integrity of microbial membranes, effects on the enzymatic systems of microorganisms, and inhibition of biofilm formation. However, laboratory results of antimicrobial activity cannot automatically be considered as confirmation of clinical efficacy. Determination of minimum inhibitory concentration, selectivity of action, local toxicity and effects on normal skin microbiota remain important.

In atopic dermatitis, promising areas include studying the effects of natural compounds on cytokine production, epidermal barrier function, and oxidative stress [8] . In psoriasis, the possibility of regulating excessive keratinocyte proliferation and pro-inflammatory signaling mechanisms is of interest. In acne, potential targets include inflammatory processes, sebaceous gland activity, and interaction with Cutibacterium acnes. In case of wound healing disorders, the most justified research is the study of the reparative, antioxidant and anti-inflammatory activity of natural components [5, 7, 10] . A separate direction is the study of plant compounds in skin pigmentation disorders [12], as well as the study of plant remedies in studies devoted to skin neoplasms [13].

However, natural substances should not be considered as an automatic alternative to standard pharmacotherapy. In particular, current clinical guidelines for atopic dermatitis are based on the use of proven agents, including emollients, topical anti-inflammatory drugs and, when indicated, systemic targeted therapy [14] .

The development of potential drugs based on natural biologically active substances requires a phased study. At the initial stage, it is advisable to establish the chemical composition of the studied substances, determine the content of the main active components, assess their stability, and standardize the methods of obtaining them [1 5].

The next stage is a screening study of pharmacological activity using various models : cellular, in vitro and in vivo. Promising directions are to determine the effect of the studied compounds on cell viability, oxidative stress intensity, expression of pro-inflammatory cytokines, proliferation and cell migration [16, 17].

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As part of the preclinical study, it is also necessary to evaluate local irritation, sensitization, and cytotoxic effects, and, if necessary, systemic toxicity [16, 17].

The pharmacological justification of the choice of dosage form is of particular importance, since the bioavailability of natural compounds depends on their physicochemical characteristics, stability and ability to penetrate the skin barrier. Modern research considers hydrogels, lipid carriers and other delivery systems as promising technological solutions, but their advantages need to be confirmed for each specific substance [7, 18]. Therefore, a promising direction is the development of standardized dosage forms for local application, capable of providing the necessary concentration of the active substance directly in the area of damage.

Thus, the analysis of modern scientific data indicates a significant pharmacological potential of biologically active substances of natural origin in the treatment of skin diseases. The diversity of their mechanisms of action, in particular anti-inflammatory, antioxidant, antimicrobial and reparative activity, creates the prerequisites for the development of new drugs for dermatological purposes. A comprehensive study of the molecular mechanisms of action of natural compounds , their effectiveness, safety and features of local application is especially promising. Further experimental and clinical studies will contribute to the scientific substantiation of the use of these substances in modern rational pharmacotherapy of dermatological diseases.

Conclusions .

1. Biologically active substances of natural origin are a promising source of pharmacologically active compounds for the creation of new drugs intended for the treatment of skin diseases.

2. The main potential mechanisms of their dermatotropic activity are modulation of the inflammatory response, regulation of oxidative stress, effects on cell proliferation, antimicrobial activity, and stimulation of reparative processes.

3. Of greatest scientific interest are flavonoids, polyphenols, terpenoids, saponins, and polysaccharides, the pharmacological effects of which are associated with the regulation of molecular signaling pathways NF-κB, MAPK, Nrf2/ARE, TGF-β, and other cellular response systems.

4. Comprehensive pharmacological research of natural compounds should include standardization of chemical

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composition, evaluation of pharmacodynamic properties, investigation of toxicological profile, and determination of optimal delivery systems.

5. Further experimental and clinical study of natural biologically active substances will contribute to the scientific substantiation of the possibility of their use as part of innovative dermatological medicines.

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