Науково-практичне фахове видання

Електронна сторінка журналу – phytotherapy.vernadskyjournals.in.ua

Видавничий дім «Гельветика» 2025

ISSN 2522–9680

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UDC 612.8.04:615.015(082)

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To cite this article: Gorchakova N., Harnyk T., Belenichev I., Hnatiuk V., Shumeiko O., Klymenko O., Gorova E., Romanova K. (2025). Syhnalni shliakhy v mekhanizmakh dii likarskykh zasobiv [Signaling pathways in the mechanisms of drug action]. *Fitoterapiia. Chasopys – Phytotherapy. Journal, 4,* 6–21, doi: https://org/10.32782/2522-9680-2025-4-6

SIGNALING PATHWAYS IN THE MECHANISMS OF DRUG ACTION

Actuality. *Signaling pathways are chains of biochemical reactions and mechanisms that process and transmit signals in response to environmental changes. They coordinate cellular and tissue functions, regulate metabolism, and influence cell growth and differentiation. Many drugs targeting the nervous, cardiovascular, and other systems exert their effects through signaling pathways, making them key pharmacological targets.*

Aim of the study. *To present the role of signaling pathways in modeling pathological conditions and in the mechanisms of drug action.*

Research methods. *Literature data on signaling pathways in pathological conditions and drug mechanisms were analyzed using sources from Scopus, Google Scholar, and other databases. Indicators confirming drug effects on signaling pathways and their capacity to correct signal transmission disturbances were also identified.*

Research results. *Well-known signaling systems and their involvement in the pharmacodynamics of neurological, cardiovascular, and oncological drugs were summarized. Pathophysiological factors influencing pathological condition modeling and signal transmission disruptions were outlined. Drugs recommended for correcting signal transport disturbances in the nervous, cardiovascular, and other systems were indicated.*

Conclusions. *Current literature emphasizes the importance of signaling pathways in explaining biochemical and pathophysiological disturbances and highlights their role as pharmacological targets.*

Key words: *signaling pathways, intracellular signaling, neurotoxicity, oxidative stress, phytotherapy, targeted therapy.*

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Бібліографічний опис статті: Горчакова Н., Гарник Т., Бєленічев І., Гнатюк В., Шумейко О., Клименко О., Горова Е., Романова К. (2025) Сигнальні шляхи в механізмах дії лікарських засобів. *Фітотерапія. Часопис, 4, 6*–21, doi: https://doi.org/10.32782/2522-9680-2025-4-6

СИГНАЛЬНІ ШЛЯХИ В МЕХАНІЗМАХ ДІЇ ЛІКАРСЬКИХ ЗАСОБІВ

Актуальність. *Сигнальні шляхи – це ланцюги біохімічних реакцій і механізмів, що обробляють і передають сигнали, реагуючи на зміни у своєму середовищі. Вони забезпечують координацію функцій клітин і тканин, впливають на регуляцію метаболізму, ріст і диференціацію клітин. Багато препаратів, які діють на нервову, серцево-судинну й інші системи організму, реалізують свій вплив через сигнальні шляхи, роблячи їх ключовими об'єктами фармакологічного впливу*

Мета дослідження *– представити роль сигнальних шляхів при моделюванні патологічних станів і реалізації механізму дії лікарських засобів.*

Матеріал і методи. *Аналіз даних літератури щодо сигнальних шляхів у розвитку патологічних станів і механізму дії лікарських засобів за джерелами у виданнях «Scopus», «Google Scholar» тощо, а також визначення показників, які підтверджують вплив лікарських засобів на сигнальні шляхи та їх здатність коригувати порушення передачі сигналу.*

Результати дослідження. *Наведені літературні дані щодо найбільш відомих сигнальних систем, їх участь у фармакодинаміці неврологічних, серцево-судинних та онкологічних засобів. Перераховані патофізіологічні фактори, які впливають на моделювання патологічних станів і порушення передачі сигналу. Указані лікарські засоби, які пропонують призначати, з метою корекції факторів транспорту сигналів у шляхах нервової, серцево-судинної та інших систем.*

Висновок. *Наведені дані літератури підтверджують значення сигнальних шляхів для пояснення біохімічних і патофізіологічних порушень в умовах захворювань і напрям впливу лікарських засобів з поясненням їх механізму дії.*

Ключові слова: *сигнальні шляхи, внутрішньоклітинна сигналізація, нейротоксичність, оксидативний стрес, фітотерапія, таргетна терапія.*

Introduction. Actuality. Signaling pathways are circuits that transmit signals about biochemical and pathophysiological changes in the body in pathological conditions and under the influence of drugs. Understanding the mechanism of signal transmission helps to target pharmacotherapy. Signaling pathways are chains of biochemical reactions and mechanisms by which a cell receives, processes, and transmits signals, responding to changes in its environment and regulating vital processes such as growth, development, metabolism, and immune response. These pathways are the basis for the normal functioning of cells and tissues, and their disruption can lead to the development of various diseases.

The primary signaling system receives signals from the environment using the senses. Signaling systems in organs and systems may include cytokines, active groups of enzymes, receptors, ion channels, and transporters. In the nervous system, a pathogenetic factor in diseases may be violations of thiamine-dependent processes. Thiamin diphosphate is a coenzyme of several enzymes of carbohydrate metabolism, damage to whose functions leads to oxidative stress. Antagonists of thiamine through mitochondria can cause apoptosis in a non-receptor way, in the process of which the p53 protein plays an important role (Chorny & Parkhomenko, 2008).

The second signal system contributes to the formation of conditional-reflex connections, is a regulator of thinking and speech, and facilitates communication between people, influencing their responses.

Aim of the study. To present the role of signaling pathways in the modeling of pathological conditions and the mechanism of action of drugs.

Research methods. To conduct an analysis of literature data on signaling pathways in the development of pathological conditions and the mechanism of action of drugs based on sources in the publications "Scopus", "Google Scholar" and others, as well as the determination of indicators that confirm the effect of drugs on signaling pathways and their ability to correct signal transmission disorders.

Research results. Long-term memory is known to depend on the development of long-term signaling, first discovered in rabbit neurons. This process is associated with the activity of glutaminergic signals and an increase in synoptic potential. The cerebral cortex and cerebellum, as well as signaling systems associated with their activation, participate in this mechanism (Nastenko & Veselovskyi, 2021). In chronic lymphocytic leukemia, ligation of CD180 receptors causes changes in B-lymphocyte signaling pathways in 80% of cases, which is accompanied by activation of Akt or p38 MAPK, or simultaneous activation of both kinases (Gordiienko et al., 2017).

One of the most recently discovered is the P2X receptor, which belongs to the purine receptors and is present both in neurons and in glial cells of various parts of the brain. It plays a significant role in the normal functioning of the brain (Pevarello et al., 2017).

Drugs affecting P2X receptors have a special effect in inflammatory diseases. P2X receptors of different families have their own characteristics. Thus, the P2X4 receptor has a high sensitivity to adenosine triphosphate compared to P2X7 and therefore greater effectiveness in brain disorders. After conducting research, the peculiarity of the importance of purinergic receptors, especially P2X7 and P2X4, as promising drugs for the treatment of CNS disorders was emphasized (Ehorova & Maksimyuk, 2024).

Contribution to the treatment of neuroinflammatory and neurodegenerative processes, including ischemic brain damage, is noted. Treatment of P2X4 receptors with ATP, TNF, ATP has a neuroprotective effect (Ozaki et al., 2016).

These receptors can play a significant role in the development of epilepsy treatment. During an epileptic attack, the level of extracellular ATP increases. The use of P2X7-receptor antagonists reduces seizures. After a seizure, P2X7 and P2X4 are downregulated, making them targets for antiepileptic therapy (Beamer et al., 2019).

It has been shown that the release of ATP is induced by the virus COVID-19. Angiotensin-converting enzyme 2 (ACE2), which belongs to metalloproteases, promotes the interaction of the COVID-19 virus with body cells. ATP is characterized by high expression on lung alveolar epithelial cells and enterocytes of the small intestine, and it is also present in glial cells and brain neurons and microglia. The latter, like macrophages, has a high level of expression of P2X receptors, in particular the P2X7 receptor, which leads to the expression of pro-inflammatory effects with increased ATP content. Inhibition of P2X7 itself may be a target to suppress COVID-19 and help control the spread of the disease (Maliha et al., 2024).

Particular attention is paid to purinergic receptors in the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis. P2X7 receptors are of critical importance in Alzheimer's disease. The level of ATP and amyloid formations is of great importance. Now it is noted that P2X7-receptors are of critical importance in the development of Alzheimer's disease. There are conflicting data on the influence of these receptors on the activity of α-secretase. It is the blockade of P2X7 receptors that reduces the deterioration of patients' memory and prevents the death of neuronal cells under the influence of β-amyloid protein (Heppner et al., 2015).

In Parkinson's disease, 6-hydroxydopamine increases the release of ATP and its subsequent conversion to adenosine in the extracellular space due to increased expression of nucleotidases in SH-SY5Y cells. Signaling pathways in the nervous system can interrupt ion channel blockade. A model of damage to calcium channels in rat dorsal spinal cord neurons, leading to the interruption of the blockade of calcium flux by inducing artificial short-term hyperglycemia in cultured neurons of the dorsal spinal cord of rats, determined the postsynaptic current potential of SH-SY5Y human neuroblastoma.

It is known that inhibition of P2X7 receptors has a neuroprotective and neuroregenerative effect. At the same time, modifications of neuroglia and release of cytokines are activated. Overexpression of P2X4 receptors upregulates IL-6 and enhances dopamine-induced dopaminergic activity (Zhang et al., 2021).

P2X receptors, especially P2X7 receptors, are important in Huntington's disease. In this disease, an increase in the expression of these receptors is noted; the greatest increase in expression in the striatum of deceased people, where changes in this receptor were detected (Ollà et al., 2020).

Amyotrophic lateral sclerosis is associated with the expression of P2X7 receptors. In rats with hyperglycemia, the blockade of calcium current in neurons of the dorsal horn of the spinal cord led to a decrease in signals related to the utilization of glucose level (Shypshina et al., 2019).

Considering the involvement of signaling pathways, a traditional drug has been proposed in China *Jiao-Tai-Wan*. Its active component, berberine, affects protein complexes. Thanks to this, gene expression occurs, glucose metabolism signaling changes, and an immunomodulatory effect is realized, which improves glucose metabolism and the condition of patients with diabetes. (Tang et al., 2024)

It is known that the NMDA receptor antagonist memantine is prescribed for the treatment of various types of dementia, including Alzheimer's disease. In experiments on rats, it was established that memantine affects memory, which became the basis for studying its effect on calcium signals. Excessive stimulation of A-type NMDA receptors causes an intense influx of calcium ions into the cell and can lead to glutamate excitotoxicity. The NMDA receptor antagonist memantine, by blocking these receptors, reduced the influx of calcium ions, affecting calcium signaling in neurons. The NMDA receptor antagonist memantine also protected hippocampal neuronal cultures from beta-amyloid-induced calcium overload. Memantine also reliably blocks calcium channels, inhibiting signaling (Shkryl et al., 2021). The nervous system receives signals from the periphery and impulses to the visceral system. Signaling pathways ensure homeostasis, physical status, behavior and consciousness, division of actions into conscious and unconscious (Berntson & Khalsa, 2021). By affecting calcium in the hippocampus, it is possible to change signaling systems that adjust the activity of organs and systems. Thanks to the signaling pathways, the activity of the organs of the digestive tract, in particular the gallbladder, is supported (Goldstein et al., 2021). Communication is carried out by neurons of the hypothalamus. AgRP neurons are involved in this.

At the same time, modern science pays attention to afferent signals and signaling pathways associated with the system of receptors located in internal organs. It is the identification of descending and ascending signaling pathways that allows us to determine the functioning of the organism (Berntson & Khalsa, 2021). The function of signaling pathways has been established thanks to physiologists, pathophysiologists, endocrinologists and doctors. But mathematicians and physicists also took part in discovering their structure. The difference in the structure and function of blocking signals of the peripheral nervous system and internal organs was established (Luo, 2021). Signal pathways in mental illnesses were also studied by psychiatrists and neurologists. Signaling pathways in Parkinson's disease were investigated using magnetic oscillography, which allowed studying the connection between the motor area and the subthalamic nuclei (Oswal et al., 2021). The study of the transcription of mitogenic signals became the basis for the creation of targeted antitumor agents. The first antitumor agents were aimed at dysregulation of signal transduction during tumor growth as a manifestation of uncontrolled proliferation. This made it possible to start the development of anticancer therapy taking into account the key features:

1) autonomy of growth signals;
2) deviation from the action of growth inhibitory signals;
3) inhibition of apoptosis;
4) unlimited replication potential;
5) distorted angiogenesis;
6) susceptibility to ischemia and metastasis.

It turned out to be possible to find signaling pathways that are important for tumors, but not critical for the normal functioning of the body, signal transmission cascades, the influence of which became the basis for the creation of drugs that act on a molecular target – separate links of the pathogenetic chain of the neoplastic process. Most anticancer agents have specific targets. Drugs of targeted action (targeted therapy) were obtained in order to influence the growth of tumors according to a special condition, taking into account the state of signal transduction associated with:

1. recognition and binding of a signaling growth factor;
2. internalization – when the signal enters the cell;
3. penetration of signals into the cell nucleus and activation of transcription factors of specific genes that respond to signal commands for proliferation, differentiation, repair and apoptosis.

Signal transmission is carried out with the help of proteins; possible reactions are phosphorylation and dephosphorylation. The family of epidermal growth factor receptors (EGF-R, EFR/EGFR) takes the leading place among the regulatory factors, a universal receptor that leads to the stimulation of the growth of many types of cells. Endothelial growth factors exert their effects through a membrane receptor that belongs to the ErbB family – universal receptors that stimulate many types of tissues. The EGFR family includes, in addition to the receptor itself, Tof (α-regulin), marine-binding EGF, growth factor-like, β-cerulin, epiregulin, and guregulin. All members of the family have common structural features. One or more EGFRs exert their effects via the membrane receptor ErbB, which belongs to a family of four receptor subunits that can be simultaneously activated:

1) human growth factor gene;
2) human avian erythroblastoma virus homeo-oncogene (v-erbB);
3) genome first isolated from rat neuroblastoma cells.

The deciphered structure of the membrane receptor contains a large transmembrane glycoprotein with a molecular weight of approximately 170.000 Daltons. The product of one of the oncogenes, the receptor-binding ligand, has two cysteine residues that stabilize the secondary structure of the domain, as well as two glycine-rich globular domains responsible for recognizing specific ligands. Near the transmembrane helix of membrane receptors is the membrane regulatory enzyme of the cell – the ATP-bound part of the regulatory subdomain. This enzyme phosphorylates various cellular subdomains. Regulatory fragments contain threonine and serine residues that can be phosphorylated by intracellular proteins, including protein kinase C and other mitochondrial enzymes. 4–5 threonine residues, which are autophosphorylated by an intracellular kinase, were found in the c-cell region of the BrfR molecule. It is these fragments that activate protein effectors or adapters that ensure the transmission of regulatory signals. The study of regulatory signals not only contributes to the study of signaling pathways and the effect of various drugs on them, but also helps to create drugs, including antitumor drugs, which have reasonable targets (Sharykina et al., 2014).

There is a group of traditional cytostatics and their combinations that affect biotechnological processes in tumor cells at the genomic level. Currently, the search for targeted (molecularly directed) drugs capable of affecting the transmission of pathological mitogenic signals and the genome is underway. These studies are related to the study of signaling pathways in triad and malignant tumors, in particular, a signaling pathway that transmits information to embryonic cells and is necessary for differentiation, the Hedgehog signaling pathway. The role of the Hedgehog signaling pathway in influencing the malignant cells of medulloblastoma, prostate, lung and thymic cancer has been shown, which has sparked interest in this signaling system as a target for finding approaches in cancer treatment. The Hedgehog gene was identified during a study of fruit fly genes. Because the embryo had teeth resembling a hedgehog, it was named Hedgehog. The main components of the signaling pathway include the Sonic Hedgehog ligand, the receptor – a receptor-like seven-helical transmembrane protein that belongs to G proteins, and transcription factors. There are three main transcription factors, one of which is associated with glucose.

The key to signal transduction is the Smo protein, whose function is inhibited in the absence of SHH – the transmembrane protein Patched. When SHH binds to it, the inhibition is lifted, allowing Smo to signal more actively. In general, the activated signaling of the Hh pathway with the transmission of mitogenic signals is manifested in the hyperexpression of the main links of the transmission of mitogenic signals during tumor growth, which determines the search for means of treatment for patients with malignant neoplasms. Now more than 200 compounds have been identified that can affect this signaling pathway as antagonists (Sharykina, Puskov et al., 2020).

In recent decades, the intracellular signaling system has been widely studied: from the interaction with the ligand-receptor to translation and post-translational processes. Dysregulation of these pathways is the basis of a number of human pathological conditions, including malignant neoplasms. Oncopharmacological studies are devoted to the dysfunction of the main signaling pathways involved in the control of cell proliferation, differentiation, migration, cell defegulation and apoptosis: ErbB, EGFR, Hedgehog transduction cascade, Wnt, TGF-β, HFS and others.

The mechanism of action of target drugs is determined taking into account the establishment of the interaction of signaling pathways. It has now been shown that hypozoline derivatives are not inferior in their antitumor effect, and sometimes exceed the activity of the world standard in non-small cell lung cancer – erlotinib, a target-type quinazoline derivative. New compounds, like previous drugs, are able to block the EGF (epidermal growth factor) production cascade at the level of its receptor, EGFR.

The study of Hedgehog (Hh) signaling made it possible to obtain compounds that block signals at the level of the Smo cascade, not inferior to the action of the standard compound Cyclopamine. The Wnt signaling pathway also controls many cellular processes; dysfunction of this pathway is associated with a wide range of human pathologies, including the development and progression of malignant tumors, such as lung cancer, colon cancer, medulloblastoma, and glioblastoma multiforme. The name of the Wnt cascade is derived from a combination of the gene name Wingless (Wg) in the Drosophila fruit fly and Int-1 in the mouse – Wnt for short.

To transmit Wnt signals inside the cell, the Wnt ligand binds to the corresponding receptor or a group of receptors – Frizzled (Fz). Fz proteins are a large group of G protein-coupled receptors (GPCRs). In addition to Fz receptors, there are other proteins on the cell surface that can bind to the Wnt protein. Among them is the family of LRP receptors, which transmit the Wnt signal inside the cell. Antagonists and agonists that stimulate or inhibit Wnt signaling also bind to Wnt. Three signaling cascades activated by Wnt signals are now known: the canonical (β-catenin) pathway and two non-classical pathways, which include the Wnt/Ca^{2+} signaling pathway and the PCP cell polarization pathway.

The canonical Wnt pathway is involved in a wide range of pathological processes, regulation of proliferation and differentiation, and maintenance of the stem cell population. Violation of the activity of the canonical Wnt signaling pathway is observed in many oncological diseases. Proto-oncoproteins involved in β-catenin signaling are key participants in the canonical Wnt/β-catenin cascade. In the absence of an active signal, the concentration of β-catenin in the nucleus and cytoplasm remains low thanks to a special protein destruction complex that includes the proteins Axin, APC and GSK-3β (glycogen synthase-kinase 3β).

As part of the destruction complex, β-catenin is phosphorylated with subsequent degradation. When a cell receives a Wnt-ligand signal, it binds the signaling receptor Fz, which activates Dishevelled and inhibits the destruction complex Axin, which normally controls the level of β-catenin in the cell. The specified deviations of Wnt-signaling during tumor growth also apply to tumor stem cells. Focusing on the Wnt signal, its pathogenic pathway in the case of malignant neoplasms makes it possible to develop targeted approaches that are crucial for controlling the growth of malignant tumors (Sharykina, Puskov et al., 2020).

Long-term oxidative stress can be accompanied not only by mental disorders, but also by serious problems with physical health – not only by the appearance of metabolic syndrome, but also by disorders of the cardiovascular and digestive systems. It affects tumor necrosis factor (TNF-α) and C-reactive protein. The body's response system coexists with intracellular structural disorders, which is important in their development. Transcription factors stimulate the expression of genes related to oxidative stress in the small intestine.

It is known that the development of oxidative stress is observed during stress. This is accompanied by an increase in free radicals, anion radicals, an increase in the activity of monooxygenases and NO-synthase, disruption of the respiratory chain of mitochondria and changes in the concentration of NADH. Antioxidant activity decreases and pro-oxidant activity increases, which is associated with an imbalance in the regulation of NO synthases and their ratio index.

The ability of propyl gallate and sulfasalazine to limit oxidative stress not only in the body of rats, but also in the tissues of the small intestine under conditions of oxidative stress indicates the possibility of using modulators of the NF-κB and Nrf2 signaling pathways to prevent complications in the small intestine (Mukvich et al., 2022; Ryabushko et al., 2023).

In juvenile arthritis, gene polymorphism (changes in the nucleotide sequence) is observed, which is associated with disorders of innate and adaptive immune reactions. This, in turn, changes the functioning of the intracellular components of the JAK signaling systems, which ensure the activation of the ligand-dependent JAK-STAT pathway and the family of cysteine proteases – caspases. Intracellular signaling pathways mediate the activation of caspases, central regulators of genes involved in the control of inflammatory processes and immune functions. The same complex also includes the activation pathways of NF-κB, which is regulated through kinases in the composition of multimolecular complexes.

The NF-κB (nuclear factor kappa-B activated in B cells) signaling pathway acts as a key intracellular regulator involved in the onset and development of immunoinflammatory diseases. Its activation involves intracellular factors, such as tumor necrosis factor α (TNF-α), interleukins IL-1β and IL-6, as well as matrix metalloproteinases. Activation of NF-κB promotes cell proliferation and increases the expression of markers of the inflammatory response, in particular adhesion molecules (ICAM), and also stimulates the activity of fibroblasts and fibroblast-like synoviocytes, which support the pathological process. This is accompanied by a decrease in apoptosis and increased invasiveness of cells, which contributes to the progression of the inflammatory lesion.

Stimulation of the aberrant Hedgehog signaling pathway is associated with the development of various malignancies, including gliomas. Naringenin exhibits an antitumor effect, in particular due to its influence on signaling pathways, modulation of fibroblast activity and reduction of expression of glioma tumor cells (Sargazi et al., 2021).

Vascular endothelial growth factor (VEGF) is a key signaling system involved in tumor growth. This is why anticancer drugs and immunotherapy should affect this signaling system (Niu et al., 2022).

Now a new system of bioregulators – gas signaling molecules – is being identified. These include nitrogen oxide, carbon monoxide, hydrogen sulfide, and the signaling role of sulfur dioxide and reactive oxygen species, in particular hydrogen peroxide, is discussed (Sukmansky, 2019).

Nitric oxide affects the activity of NO-synthase: neuronal (type I), inducible (type II) and endothelial (type III). It can alter the functioning of hemoglobin, myoglobin, cytochrome c oxidase and cytochrome P450. The substrate for the formation of NO is L-arginine and its derivatives (Sukmansky & Reutov, 2016).

Carbon oxide is formed as a result of heme catabolism under the action of heme oxygenase: inducible and constitutive. The substrates are heme in hemoglobin and other heme-containing proteins. Hydrogen sulfide is synthesized from L-cysteine and D-cysteine with the participation of the enzymes cystathionine-β-synthase, cystathionine-γ-lyase, 3-mercaptopyruvate-sulfurtransferase in interaction with cysteine amine transferase. D-cysteine can be metabolized with the participation of D-amine oxidase.

Polysulfides are synthesized with the participation of 3-mercaptopyruvate-sulfurtransferase in the presence of 3-mercaptopyruvate, which is formed from L-cysteine or D-cysteine. Sulfur dioxide is produced by enzymes involved in sulfur metabolism, including cysteine dioxygenase, sulfite oxidase, and thiosulfate reductase. Indirectly, transaminases such as aspartate aminotransferase and glutamate-oxoacetate-transaminase can participate in the synthesis through the exchange of sulfur-containing metabolites. The main substrates for the synthesis of polysulfides and sulfur dioxide are L-cysteine and derivatives of sulfur-containing amino acids. The substrates for synthesis are L-cysteine (Sukmansky & Reutov, 2016; Sukmansky, 2017).

Summarizing the role of gas signaling systems in the physiology and pharmacology of humans and mammals, it should be emphasized that they have a neuroprotective effect and contribute to the search for methods of eliminating memory disorders. Gaseous signaling systems dilate blood vessels, inhibit platelet aggregation and thrombus formation, and inhibit the development of atherosclerosis and hypertension. They have a pronounced effect on the protective function of leukocytes and the regulation of inflammatory processes.

Since synthesis enzymes are present in many organs and systems, gas signal molecules are involved in the pathogenesis of organs of the respiratory, digestive, nervous, reproductive and other systems. Their influence on the development of neoplasms is significant, but less pronounced (Sukmansky, 2017).

Data from the literature indicate that gas signal systems are a general biological system of bioregulators inherent in all living organisms. Determining their role may be useful for the discovery of new signaling pathways and their use in applied, medical and related fields. Studying the functions of gas signaling systems in the pathogenesis of pathological processes increases the possibilities of treatment and prevention of diseases through the use of gas signaling systems, their donors, precursors and inhibitors. The substrate for these systems is sulfur-containing amino acids, most often L-cysteine.

Polysulfides are synthesized from hydrogen sulfide, while sulfur dioxide is a sulfite anhydride formed by the oxidation of H_2S. The end product of the oxidation of the latter is sulfate, which the intestinal microflora can reduce to hydrogen sulfide. In general, there is an H_2S cycle in the body.

The known signaling function of H_2S is to promote the induction of long-term potentiation in the hippocampus of rats through increased activity of NMDA receptors. Compared to NO, H_2S has a much higher solubility. The molecular structure of H_2S is similar to H_2O, but unlike water, it does not pass through water channels and is able to overcome the lipid bilayer of cell membranes. Hydrogen sulfide, like other sulfur-containing compounds, is a toxic gas, its toxicity is 5 times higher than that of CO.

Endogenous H_2S in the body of humans and animals is synthesized from sulfur-containing amino acids, primarily L-cysteine and its oxidized form, cystine. With the participation of D-amino acid oxidase, H_2S acts as a neuromodulator and exhibits a powerful neuroprotective effect. H_2S contributes to the induction of long-term potentiation in the hippocampus as a result of activation of glutamate receptors. This effect is associated with Ca^{2+} channels and plays an important role in memory and learning processes. Impaired production of H_2S is observed in neurodegenerative diseases such as Alzheimer's and Parkinson's.

Inhalation of H_2S can inhibit blood disorders by penetrating the blood-brain barrier and reduce the development of cerebral edema. The cardiovascular system is an important target for H_2S. The site of vasorelaxant action of H_2S is the blockade of calcium (Ca^{2+}) channels and the increase of NO production by the endothelium. The mechanism of the vasodilatory action of H_2S is complex and is associated with the formation of nitroso-myoalds, the opening of potassium channels, the reduction of ATP content, the inhibition of metabolism, the regulation of angiogenesis, and other processes.

Platelets, as part of vessel walls, produce H_2S. There are data on the positive effect of H_2S in lung diseases – it inhibits acute hypertoxicity. H_2S is important in the kidneys and urinary tract. Enzymes of H_2S synthesis were also found in the liver. H_2S is used in sanatorium-resort conditions, in particular for sulphide baths. Sulfur oxide (SO_2), as a gas signaling system, is a toxic gas and a known environmental pollutant. When inhaled, it can cause coughing. SO_2 dissolves well in water, in the blood plasma it can be transformed into sulfate and sulfide derivatives. Like NO and H_2S, SO_2 can improve blood pressure, alter heart rhythm, and participate in inflammatory responses. Endogenous SO_2 is synthesized in many organs and tissues. Metabolic effects of H_2S include regulation of renin content, inhibition of angiotensin-converting enzyme, stimulation of angiogenesis, and inhibition of atherosclerosis. In interaction with NO and SO_2, H_2S acts protectively on the myocardium. In experimental atherosclerosis, lipid metabolism and SO_2 synthesis were disturbed. SO_2 is also involved in the pathogenesis of neurological disorders. The optimal function of polysulfides and H_2S extends to many body systems, best studied in the nervous system. It was established that tri- and tetrasulfides cause a signal entry of Ca^{2+} into the cells of the nervous and cardiovascular systems. Polysulfides are a typical form of bound sulfur in the redox regulation system. The bound sulfur H_2S is incorporated into proteins as persulfide or polysulfide. The mechanism of increased calcium entry by polysulfides is related to the activation of TRPA1 receptors in gastrocytes and can be inhibited by their effective inhibitors. Polysulfides perform a neuro– and cardioprotective function. They increase the permeability of endothelium and albumin. Donors of polysulfides can reduce the content of serotonin, and most importantly, have a neurotropic and cardiotropic effect (Sukmansky & Reutov, 2016).

Hydrogen peroxide and other reactive oxygen species can be formed in many types of cells during phagocytosis in neutrophils, monocytes, and macrophages, as well as in the process of stimulation and proliferation of bone marrow cells, lymphocytes, astrocytes, neurons, fibroblasts, and endothelial cells. In various pathological conditions, these processes can either be intensified or inhibited. Disturbance of the balance between oxidants and antioxidants in the response of cells in tumor formation, autoimmune, allergic and proinflammatory diseases, intoxications, vascular and liver diseases was noted.

Reactive forms of oxygen generated in the process of cell stimulation can affect the cells that produce them. In normal and pathological conditions, human and animal cells can be exposed to hydrogen peroxide. Given that cytokines and NO are required for reactivation, the effects of nitric oxide on H_2O_2 and NO levels were investigated. The level of interleukin-1β and the total output of nitrates – the end products of NO conversion – were found to be approximately 10^4 micromoles 24 hours after stimulation, and the increase in NO was about twofold. Thus, hydrogen peroxide is one of the products of metabolism in organs and tissues and participates in intracellular signaling, performing the function of a signaling molecule in immune cells (Kulahava et al., 2007).

Glioma is one of the most dangerous tumors. Despite the use of antitumor therapy, it was considered appropriate to find a drug that affects the Hedgehog signaling pathway. Naringenin has antiproliferative and antitumor effects. It is known to have antitumor, antiproliferative and antihypertensive activity, and affects S6 and β3 fibroblasts. It affects the migration of S6 cells. The drug Naringenin has a significant toxic effect, affects S6 cells and causes apoptosis. It is considered appropriate to use Naringenin in the glioblastoma treatment scheme (Sargazi et al., 2021).

Traditionally in China, a decoction of the Jiao-Tai-Wan plant is used. As it was established, the decoction affects signaling pathways and has an immunocorrective effect. This tool improves the increased expression of macrophages, lowers the level of IL-1β, IL-6, TNF-α, P6S2, VE6P. The obtained data indicate the antitumor effect of the decoction (You et al., 2023).

Chinese plant Pai Nong Sang has long been used to treat colitis and colorectal cancer. This plant has an anti-inflammatory and immunostimulating effect. In addition, its extract affects Wnt signaling pathways. Thanks to the immunomodulatory effect, the drug restores the content of interleukins, improves it tumor necrosis factor and the state of the gut microbiome (Yang et al., 2014).

In recent years, considerable attention has been paid to the possibility of the effect of plant components or phytopreparations in general on cell signaling pathways. The most famous studies in this direction were conducted using herbal remedies of traditional Chinese medicine. These agents have been found to contain active substances, including phosphatidylinositol-3 protein kinase (PI3K) and protein kinase B (Akt), which can affect signaling pathway substrates such as the transcription factor FOXO3, glycogen synthase kinase-3β (GSK-3β), and caspase-9. This explains the neuroprotective effect of plant active substances and provides grounds for including them in complex pharmacotherapy of Alzheimer's and Parkinson's disease (Long et al., 2021).

The neuroprotective activity of the combined herbal preparation, which includes extracts, was established on the model of scopolamine disturbance of the activity of the nervous system *Gastrodia elata* Blume, *Polygala tenuifolia* Willd., *Desert Cistanche* And, *Rehmannia glutinosa*, *Acorus gramineus* Aiton ta *Turmeric is long* L. This herbal preparation can model dopaminergic synapses and apoptosis of hippocampal signaling pathways. It is recommended to include this phytoremedial agent in the treatment of Alzheimer's disease (Huang et al., 2022).

Due to the fact that the mechanism of neuroinflammation may be involved in neurodegenerative diseases, the effect of a plant extract of 32 components on the NF-κB signaling pathway was established, which leads to a decrease in inflammatory processes in the nervous system (Bai et al., 2021). Parkinson's disease is treated with the inclusion of phytoremedies obtained from China and India and can affect topominergic neurons, and can affect signaling pathways such as PI3K, NF-κB, AMPK (Yin et al., 2021). Traditional herbal preparations are prescribed to patients with increased excitability, as well as symptoms of depression, which is associated with the effect on such signaling pathways as AKT1, IL-6, TNF, PTGS2, JUN, CASP3, MAPK8, PPARγ, NOS3 (Pan et al., 2022). Treatment of depression with plant extracts is associated with effects on the level of pro-inflammatory cytokines and the GABA-ergic system and signaling pathways of GAD-1, VGAT and others (Zhang et al., 2021). To a large extent, the positive effect of Chinese herbal preparations on the CNS is associated with a decrease in neurotoxicity and oxidative stress due to the influence on the PI3K/Akt/Nrf2 and TLR4/NF-κB signaling pathways, which is accompanied by a decrease in the levels of pro-inflammatory cytokines IL-1β, IL-6, TNF-α and the activation of antioxidant mechanisms. Reduction of neurotoxicity and oxidative stress is also associated with the effects of Chinese plant extracts on JAK2/STAT3 signaling pathways (Lv et al., 2021).

Chinese plant extracts help prevent and treat stroke by affecting PI3K/Akt signaling pathways (Liu et al., 2022). A possible effect in the prevention of stroke cases is carried out through JAK/STAT, NF-κB, MAPK, Notch, Nrf2 signaling pathways (Li et al., 2022). There are references to recommendations to include extracts of Chinese plants in the treatment regimen of atherosclerosis, especially in the presence of Salvia miltiorrhiza (Yang et al., 2023). In experiments on rats with a simulated myocardial infarction, the protective properties of a decoction of Chinese plants, a normalizing effect on protein kinase activity and indicators of oxidative stress, as well as an effect on signaling pathways were established (Yu et al., 2023).

Extracts of Chinese plants are used in the treatment of diseases of the digestive organs. Their effectiveness in the treatment of ulcerative colitis is unknown. At the same time, the active substances affect such signaling pathways as PI3K/AKT, NF-κB, JAK/STAT, MAPK and Notch (Zheng et al., 2022). The plant extract is prescribed for various inflammatory diseases, including the digestive tract due to its influence on the JAK/STAT signaling pathways (Chen et al., 2022). Saponins contained in extracts of medicinal plants can have an antitumor effect in different localization of tumors (Zhu et al., 2023). Extracts of Chinese plants are recommended for use in inflammatory liver diseases, which is associated with receptor influence and action on NLRP3 signaling pathways, effective in liver diseases (M.-x. Pan et al., 2021). Plant extracts are effective in tissue damage by srotadriamycin. Their effect is also related to CAMKK2/AMPK signaling pathways (Zhang et al., 2023). Include extracts of Chinese plants in the complex treatment of pancreatic cancer. At the same time, the impact on JAK-STAT, NF-κB, MAPK, PI3K-AKT signaling pathways is noted (M. Li et al., 2022). Herbal preparations were also used to treat obstructive lung diseases. Their effect is related to the effect on protein kinase, TNF and MPKA signaling pathway (J. Li et al., 2021). Chinese herbal preparations were also tested in case of fibrotic kidney disease. Their effectiveness is related to the impact on the MAPK, PI3K-AKT, and TNF signaling pathways. Decoctions of Chinese herbal medicines are also recommended for chronic bronchitis. Their effectiveness is confirmed by the effect on TNF, MARK, PI3K-AKT signaling pathways (Yuan et al., 2020).

The effectiveness of Chinese plant extracts in bronchitis is realized due to JAK-STAT signaling pathways (Ding et al., 2025). Due to the ability of phytopreparations to reduce oxidative stress-induced damage, these drugs are recommended for exposure to exogenous toxins associated with the Nrf2 signaling factor (Molaei et al., 2021). By affecting the epidermal growth factor, phytoremedies are prescribed in the complex treatment of lung cancer, while they affect the EGFR-tyrosine kinase (Lee et al., 2021). Phytopharmacological agents have been successfully included in the pharmacotherapy of lung cancer by targeting apoptosis, micro RNA, the BRCA-1 gene, the P53 protein, the P13K/Akt/mTOR signaling pathway, the Notch signaling pathway, the Hedgehog/Gli-1 signaling pathway, poly-ADP ribose polymerase inhibitors, and MAPK inhibitors (Singh et al., 2021). An extract from the plant Qi-Qin-hu-chang is recommended for the treatment of colorectal cancer (Wu et al., 2023).

Chinese medicine agents are used to treat hepatitis B by targeting signaling pathways such as JAK/STAT, PI3K/Akt, NF-κB, MAPK (Zheng, Qi, et al., 2024). An extract from Chinese plants is prescribed in the presence of androgenetic alopecia (Jinjin et al., 2022). Extract from Chinese plants is very useful for non-alcoholic liver diseases. At the same time, the signaling pathways of NAFLD, PPAR, AMPK, and NF-κB are taken into account (X. Zhang et al., 2024). especially alkaloids are useful in Chinese plants for the treatment of acute kidney diseases. It is alkaloids that activate the Nrf2/HO-1 signaling pathway (Rui et al., 2022).

It is considered appropriate to include herbal preparations of Chinese medicine for the treatment of chronic inflammatory bowel diseases, including Crohn's disease (S. Yuan et al., 2022). Gastric cancer therapy may include an herbal preparation from Rabdosia rubescens, affecting signaling pathways of TNF-α, TGF-β, and androgen receptor (Gao et al., 2023).

Means of Chinese medicine have significant anti-inflammatory activity, which is the basis for the creation of new drugs. In addition, they have a neuroregenerative effect, inhibiting inflammation and oxidative stress. This allows them to be included in pulmonary fibrosis treatment regimens by influencing TGF-β signaling pathways (Z. Wu et al., 2022).

More and more herbal anticancer agents are being created. Special importance is given to polyphenols. They affect atherosclerosis and key signaling pathways (Jenča et al., 2024). For spinal injuries, it is recommended to take an extract from Chinese plants, which improve metabolism in the surrounding tissues and affect the signaling pathways of mTOR, SCI, MITOR (Y. Ding & Chen, 2022). Antioxidant herbal preparations are recommended to be included in treatment regimens for liver fibrosis due to their effect on the β-catenin signaling pathway (Cheng et al., 2023).

Thus, various signaling pathways not only ensure the vital activity of organs and systems, but also play an important role in the mechanisms of development of pathological processes, the influence of which determines the targeted effect of modern drugs.

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Стаття надійшла до редакції 22.08.2025
Стаття прийнята до друку 30.10.2025
Опублікована 29.12.2025

Conflict of interest: none.

Gorchakova N.O. – data collection and analysis, article writing, critical review, final approval of the article;
Harnyk T.P. – concept and design of the work, article revision, critical review;
Belenichev I.F. – data collection and analysis, article revision, conclusions;
Hnatiuk V.V. – data collection and analysis, article revision, conclusions;
Shumeiko O.V. – data collection and analysis, annotations, participation in article writing;
Klymenko O.V. – data collection and analysis, summary, participation in article writing;
Gorova E.V. – data collection and analysis, article revision, conclusions;
Romanova K.B. – data collection and analysis, summary, participation in article writing.

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