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Natural Polyphenols: Biological Activity, Pharmacological Potential, Means of Metabolic Engineering (Review)

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Abstract—This review examines the main features of natural phytoalexines of flavonoid and stilbenoid natures, which are secondary metabolism products in numerous plants widely used as biologically active substances in the medicine, pharmacology, and agricultural plants protection. We considered the role of flavonoids and stilbenes in phytoimmune and antistress responses in plants, bactericide antifungul, and antiviral effects towards microorganisms, and the wide medical application for a number of mammalian pathologies. The main achievements in the metabolic engineering of flavonoids in microbial biotechnologies are discussed.

Keywords: polyphenols, flavonoids, stilbenes, phytoalexines, metabolic engineering

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INTRODUCTION

Polyphenols are products of the secondary plant metabolism that are widely used as biologically active compounds in pharmacology, medicine, and agriculture. Phenolic compounds were found in all organs of the most diverse plants (fruits, seeds, roots, bark, wood, and leaves). More than 8000 different phenolic compounds were identified in plant tissues. The breadth of their distribution in the plant kingdom determines the diversity of their chemical structure. Phenolic compounds exist in plants in the form of monomers, oligomers, polymers, and they are represented by simple phenols, hydroxycinnamic and hydroxybenzoic alcohols, aldehydes and acids, flavonoids, stilbenes, and lignans and their derivatives, tannins and lignin [1, 2]. Flavonoids are one of the most numerous classes of natural phenolic compounds represented by polyphenols with a structural base consisting of a flavone ring containing two aromatic rings connected by the C_3 bridge (Fig. 1a) [3]. Catechins, leucoanthocyanins, anthocyanins, flavonones, flavones, flavonols, chalcones, etc., are allocated based on the ring structure [4, 5]. Flavonoids are widely represented in various vegetable crops, fruits, flowers, seeds, and tree bark (Table 1) and are therefore an important part of the diet of animals and humans [6]. Stilbene compounds, which are structurally and functionally related to flavonoids phenolic compounds with two benzene rings, are the part of polyphenol group. Stilbene compounds were found in many plant species, including coniferous trees; they are natural phenolic protective compounds with antimicrobial activity towards phytopathogens and antioxidant activity towards oxidants-ozone and ultraviolet irradiation (Table 2) [7, 8]. The main representatives of the class of stilbenes are resveratrol, pterostilbene, pinosylvin, rhaponticin widely used in modern pharmaceutics, medicine, and industrial technologies [3]. A typical representative of the class is stilbene (Fig. 2b), which is widely used in scintillation counters, and its derivatives are used as dyes, optical brighteners, antitumoral agents, and artificial hormones with high estrogenic activity. Stilbenes attract much attention due to their wide range of activities. They exhibit antioxidant, antitumoral, anti-inflammatory, antibacterial, antiviral, and antimalarial properties and inhibit various pathological processes. Stilbenes exhibit neuroprotective properties upon neurotoxic glutamate effects and brain damage at cerebral ischemia, and their hepatoprotective properties were also revealed [8, 9]. Stilbenes were shown to be able to inhibit a number of enzymes that are activated during inflammatory reactions [10].

According to their functional properties, stilbenes and flavonoids belong to a large class of the plant antibiotics phytoalexins. Phytoalexins are components of the plant protection system against diseases capable of inactivating microbial pathogens. The special attention of researchers in these compound classes is due to their unique antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, cardioprotective, anticar-

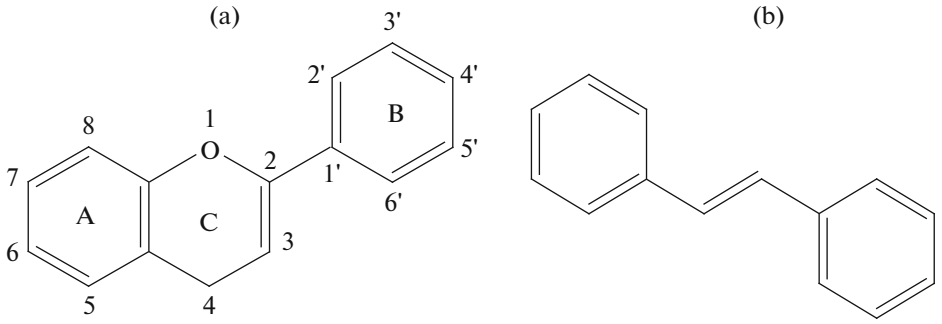


Fig. 1. Structure of flavonoids (a) and stilbenes (b).

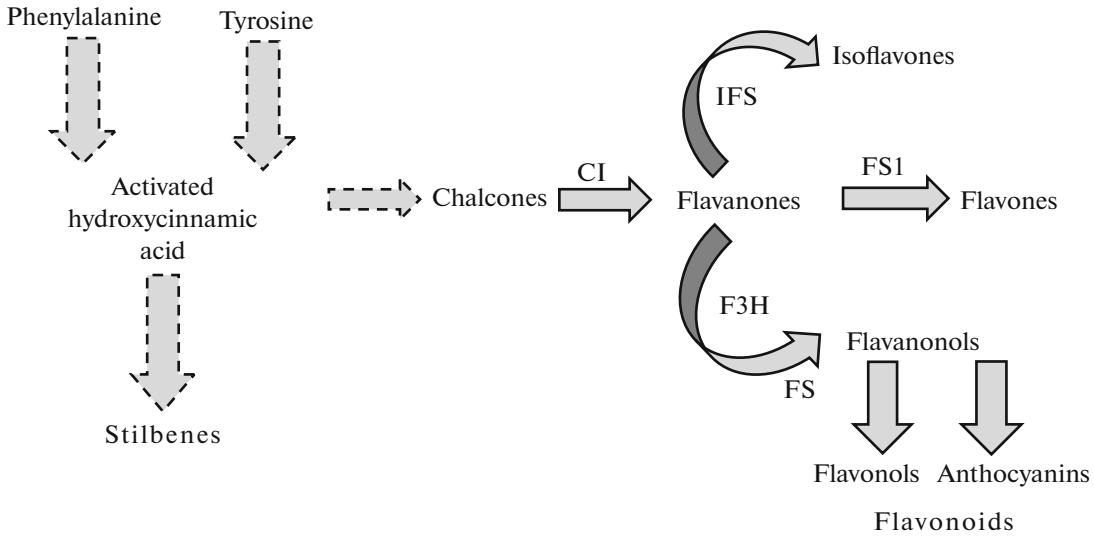


Fig. 2. Scheme of biosynthesis of natural flavonoids and stilbenes. CI—chalcone isomerase; FS1—flavone synthase 1; IFS—isoflavone synthase; F3H—flavonone-3β-hydrolase; FS—flavonol synthase.

cinogenic, and antidiabetic properties exhibited by individual representatives.

This review is devoted to the characteristics of the biological activity of phytoalexins of flavonoid and stilbene natures in various systems, the main mechanisms of their action, and the possible methods of application in modern science, medicine, and bioengineering.

GENERAL CHARACTERISTICS OF PHYTOALEXINS OF FLAVONOID AND STILBENE NATURES

Flavonoids are a group of natural compounds that includes more than 8000 representatives, and this list is constantly replenished [6, 11, 12]. Flavonoids are not only widespread in nature, being products of the secondary plant metabolism, but are also present in plant-derived products such as red wine, honey, tea, various fruits and berries, seeds, bark, and tree wood [12]. Chemically, flavonoids are a 15-carbon skeleton containing two benzoic rings (A and B, as shown in Fig. 1a), connected by a heterocyclic pyran ring (C) (Fig. 1a). The flavonoid group consists of several classes: flavones, flavonols, flavonones, catechins, leucoanthocyanins, anthocyanins, and chalcones (Table 1). Different classes of flavonoids differ in the oxidation level and the nature of C-ring substitution, while individual flavonoid representatives within each class differ by the type of substitution of the A and B rings [11]. The division of flavonoids into classes is based on the peculiarities of their biosynthesis in plant cells, which determines the presence of various intermediate (chalcones, flavanones, flavan-3-ols) and final (flavones and flavonols) metabolic products [13].

Flavonoids are also widely present in the form of aglycons, glycosides, and methylated derivatives. The basic flavonoid structure is an aglycone (Fig. 1a). The six-membered ring is condensed with a benzoic ring, either in the form of α-pyrone (in flavonols and flavonones) or its dihydroderivative (Table 1). The position of the benzoic substituent divides the flavonoid class into flavonoids (position 2) and isoflavonoids (posi-

Table 1. Distribution and main representatives of the flavonoid class

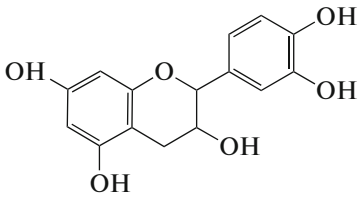
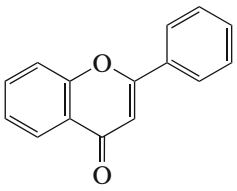
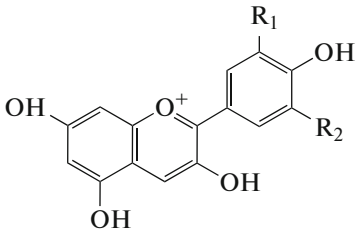
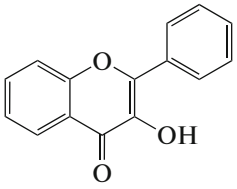
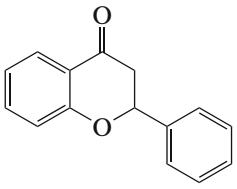
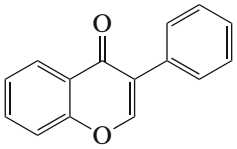
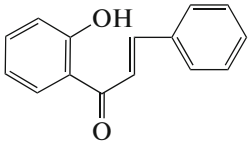
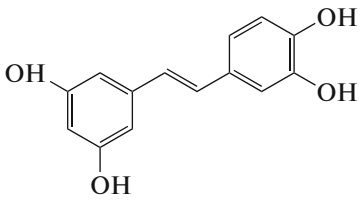
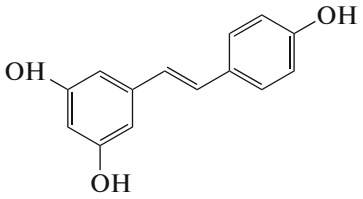
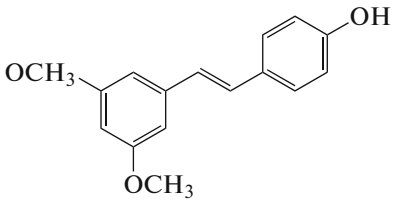
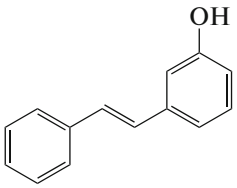
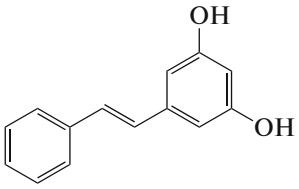
Subclass	Representative	Natural source of the compound	References
Flavonols 	(+) Catechin, (–) epicatechin, epigallocatechin	Tea	[18]
Flavons 	Rutin, luteolin, glycozides of luteolin	Fruit skin, red wine, buckwheat, red pepper, tomato	[19–22]
Anthocyanins 	Apigendin, cyanidine	Fruits of cherries and strawberries	[21, 22]
Flavonols 	Myricetin, dihydromyricetin, quercetin, dihydroquercetin, kaempferol, pinocembrin, rutin, galangin	Onions, red wine, olive oil, berries, grapefruit	[21, 23]
Flavonons 	Naringin, naringenin, taxifolin, hesperidin	Citrus fruits	[23–25]
Isoflavons 	Genistin, diadzin	Soybeans	[25]
Chalcones 	2', 4' –dihydroxyhalcone, carvacrol	*Zuccagnia punctata* *Lavandula multifidi* (lavender)	[26] [27]

Table 2. Distribution and main representatives of class of stilbenes

Representative	Natural source of the compound	References
Piceatannol (trans-3,4,3',5'-tetrahydroxystilbene) 	Sugar cane, berries, peanuts, red wine, grape skin	[28–30]
Resveratrol (trans-3 5 4'-trihydroxystilbene) 	Red wine, pistachios, peanuts, berries	[3, 16]
Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene) 	Blueberries, grapes, bark and wood of conifers	[31–33]
3-Hydroxystilbene 	*Sphaerophysa salsula*	[32]
Pinosylvin (3,5-dihydroxy-trans-stilbene) 	Family *Pinus*, and *Gnetum cleistostachyum*	[17, 34]

tion 3) (Table 1). Flavonols differ from flavanones by the hydroxyl group at position 3 and the C_2–C_3 double bond [14]. Chalcones have a noncyclic C_3-fragment (Table 1). Flavonoids are often hydroxylated at positions 2, 3, 5, 7, 3', 4', and 5'. Methyl and acetyl esters of an alcoholic hydroxyl group are also widely occur. During glycoside formation, the glycosidic bond is usually formed at position 3 or 7, and the carbohydrate component can be L-rhamnose, D-glucose, glucorganose, galactose, or arabinose [15]. Distribution in plants and typical representatives of phytoalexins of flavonoid nature are presented in Table 1.

Stilbenes are low molecular weight (Mr = 210–270) compounds of a polyphenolic nature that are widely distributed in nature in plants: grapes, blueberries, and other plants [16]. Structurally, stilbenes have a basic carbon skeleton, C_6–C_2–C_6, that includes two phenyl groups connected by an ethylene bridge (Fig. 1b). Stilbenes exist as E and Z isomers, depending on the location of the functional groups relatively to the double bond [17]. The Z-form of stilbenes (trans-orientation of molecules) has a higher antioxidant potential in animal models [17]. The distribution of the most significant representatives of stilbenes is presented in Table 2.

BIOLOGICAL ACTIVITY OF FLAVONOIDS AND STILBENES

Functions of flavonoids and stilbenes in plants. Flavonoids play an important role in the life of plants, serving as messengers in the interaction of plants and the environment [35]. These compounds are able to regulate the transport of phytohormone auxin, creating its gradient in plant cells and thus causing the formation of various morphoanatomical phenotypes [36]. For example, shaded plants, which are rich in kaempferol or apigenin derivatives, have long internodes and a large lamina in combination with reduced leaf thickness, which allows them to use solar radiation efficiently [37]. This regulation is based on the interaction of flavonoids with the glycoproteins of the plasma membrane (PIN and MDR) involved in the movement of auxin from cell to cell [38].

Plant flavonoids also act as biomarkers of abiotic stress. The effect of abiotic stress factors on the plant leads to the development of oxidative stress, which in turn leads to the generation of excess amounts of reactive oxygen species (**ROS**). The ability of flavonoids to absorb sunlight at wavelengths corresponding to the range of long-wave (UV-A) and medium wave (UV-B) ultraviolet radiation inhibits ROS products induced by sunlight [39]. This ability to quench ROS strictly depends on the nature of the substituents in the phenolic rings of the compounds. Dihydroxyderivatives of B-ring exhibit higher antioxidant activity, while monohydroxyderivatives have a significant absorption potential for ROS generated by solar radiation [39]. With excessive sun exposure, these flavonoid properties provide plants with protection via optical screening of UV radiation. Analysis of the absorption spectra of extracts of fruit skin adapted to strong light showed that flavonols, which were mainly represented by quercetin glycosides and anthocyanins, significantly absorb light at 400–420 nm, providing cell protection from excess radiation and its consequences, along with chlorophyll and carotenoids [40, 41]. The flavonoid antioxidant activity in plant cells, as determined by the ability to quench ROS, was recently confirmed. It was found that flavonoids are localized in the nuclei of mesophyll cells and chloroplasts, where the primary production of aggressive ROS forms, including hydroxyl radicals and singlet oxygen, takes place [42].

In the course of various stress effects—droughts, soil salinity, high and low temperature stresses, and limited nutrition—there is a limited diffusion of carbon dioxide, which is required for efficient photosynthesis to the carboxylation sites. Under these conditions, there is a significant decrease in the level of antioxidant enzymes in the chloroplast, which is compensated by an increase in the synthesis of ROS-detoxifying flavonoids [43, 44]. The interaction of a number of flavonoids, in particular, rutin, directly with the heads of membrane phospholipids leads to the maintenance of membrane integrity under oxidation [45].

Phytoalexins of flavonoid and stilbene natures take an active part in the reactions of phytoimmunity. It was shown that the infection of cereal plants with pathogenic fungi of the genus *Puccinia* was inhibited by increased concentrations of glycosides of apigenin and luteolin flavonoids [46]. In addition, the flavonoid glycoside content increased by almost 50% at the initial stages of rye plant infection with spores of *Puccinia graminis*, and a specific *de novo* formation of phytoalexins of flavonoid nature occurred in plants infected with *Septoria nadorum*. This fact confirms their participation in the specific plant immunoresponse during the development of fungal pathology [46].

Plant flavonoids also act as transcriptional regulators [47, 48]. The accumulation of flavonoids in cell nuclei was observed in a number of species: *Arabidopsis thaliana*, colza *(Brassica napus),* clasping yellowtops *(Flaveria chloraefolia),* spruce *(Picea abies),* eastern hemlock *(Tsuga canadensis)* and English yew (*Taxus baccata)* [49–54]. It was suggested that flavonoids can protect DNA from UV radiation and oxidative degradation [53] and can directly or indirectly control the transcription of genes necessary for plant growth and development, including genes encoding carrier proteins of phytohormone auxin [51, 52].

Interaction of flavonoids and stilbenes with microorganisms. Flavonoid and stilbene phytoalexins are synthesized in plant organisms in response to the development of microbial infection; therefore, the detection of bactericidal activity in them is not surprising. Extracts of a number of plants rich in flavonoids have a powerful antibacterial effect [55–58]. Flavonoids with bactericidal activity include apigenin, galangin, flavone, and flavonol glycosides, as well as flavanones and isoflavone [6]. Robinetin, myricetin, and epigallocatechin have the ability to inhibit the synthesis of DNA in *Proteus vulgaris* [6]. The bactericidal effect of quercetin and apigenin on the culture of *Escherichia coli* is due to the inhibition of DNA gyrase [59].

Over recent years, studies aimed at combating infectious agents that form biofilms characterized by high multiresistance to a wide number of antibiotics, in particular, the causative agents of tuberculosis (*Mycobacterium tuberculosis*), infections of the upper respiratory tract (*Streptococcus pneumoniae*) and genital tract (*Neisseria gonorrhoeae*), carious microbiota (*Streptococcus mutans*), became very important. Some polyphenolic compounds, in particular epicatechin gallate [60] and "red wine polyphenols" (quercetin, phythesin, kaempferol, apigenin, chrysin, luteolin, resveratrol) [61], effectively inhibited the growth of biofilms formed by *Staphylococcus aureus*. Flavonoids from citrus fruits (naringenin, quercetin, sinensetin and apigenin) impaired intercellular interactions and thus prevented the formation of *E. coli* biofilms [62]. Apigenin, epigallocatechin, and oligomeric proanthocyanins

effectively affected biofilms formed by *S. mutans*, the causative agent of caries [63].

The mechanism of antibacterial activity of flavonoids is not known in detail; however, most authors discuss the multiplicity of potential cellular targets through which these polyphenols can act by covalent and noncovalent interactions with components of bacterial cells—adhesins, enzymes, and cell wall proteins. Lipophilic flavonoids are able to interact directly with bacterial membranes [64, 65].

Virtually all flavonoid subclasses are characterized by antifungal activity. Long-term studies aimed at revealing the fungicidal effect of these polyphenols against the pathogen of animals and human fungus *Candida albicans* demonstrated that the main flavonoid representatives inhibit the development of this strain in an in vitro system in concentrations from 4 to 197 μg per mL [12]. The antifungal effect of flavonoids are manifested both in the inhibition of colony growth and the destruction of the fungal cell wall and in the induction of the apoptosis in yeast culture. It is interesting to note that the effects of polyphenols acquired additivity under combined actions with antifungal compounds, in particular, the flavonoids baicalein and fluconazole had synergy in vitro towards the resistant species *C. albicans* [66].

An important discovery was the proof of the polyphenols antiviral activity. It was shown that a number of flavonoids, among which flavan-3-ols were the most efficient, selectively blocked the human immunodeficiency virus (HIV-1, HIV-2). Baikalin, which is isolated from the Chinese skullcap (*Scutellaria baicalensis*), dimethylated gardenin A, and robinetin inhibited the development of the infectious process by blocking reverse transcriptase and HIV-1 proteinase, respectively [60]. Kaempferol, luteolin, and quercetin proved to be extremely effective against herpes simplex virus (HSV) [67]. Curcumin, genistein, myricetin epicatechin gallate, and stilbene resveratrol were also effective against viral infections of different etiologies [68]. It was noted that stilbene resveratrol, which is best known as a pharmaceutical agent, also has antibacterial, antiviral, and antifungal activity. According to Chan et al. [69], resveratrol inhibits bacterial growth, causing severe hospital infections, *S. aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* at concentration of 171–342 mg in 1 mL and five strains of fungi-dermatophytes at a concentration of 25–50 mg per 1 mL. At a concentration of 15 mg in 1 mL, resveratrol inhibited the growth of the proteus (*Proteus mirabilis*), reducing virulence by affecting the transmitter protein of bacterial signaling system [70]. In in vitro systems, resveratrol was effective against 16 strains of *Helicobacter pylori* [71, 72]. At extremely low concentrations (1–10 μM), resveratrol enhanced the phagocytosis of *C. albicans* pathogen by macrophages [73] and reduced the phagocytosis of *E. coli* and *S. aureus*, acting both through the TLR-2 receptors of monocytes and independently of them. Stilben pinosilvin (**PS**) with a resveratrol-like structure also exhibited antibacterial and fungicidal activity against strains of the pathogenic fungus *C. albicans* and baker's yeast *Saccharomysces cerevisiae*, as well as pathogenic bacteria of the genera *Salmonella*, *Listeria monocytogenes*, *Staphylococcus epidermidis*, *S. aureus*, pathogenic fungus *Candida tropicalis* [74, 75].

Main mechanisms of the action of flavonoids and stilbenes. In the mechanisms of action of polyphenols of flavonoid and stilbene natures, both in vitro and in vivo, several main aspects are recognized: (1) action as antioxidants and anti/prooxidants in cellular systems by changing the ROS level via enzymatic and nonenzymatic pathways; (2) action as a regulator of transcription; and (3) participation in protein kinase signaling pathways. Polyphenols are able to exhibit their antioxidant properties through direct interaction with ROS and free radicals [76, 77], and they also prevent ROS formation by chelation of transition metals [76]. In addition, polyphenols reduce the ROS level by regulating the activity of enzymes that produce or eliminate free radicals [6, 78]. Polyphenols effectively suppressed the activity of xanthine oxidase [79, 80] and also induced the activity of antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase, NAD(P)H: quinone oxidoreductase, in rat aortic cell culture and other biological systems [78, 81]. Depending on the concentration and nature of the polyphenols and on the oxidation-reduction status of the cell, these compounds, like other antioxidants, can form H_2O_2 during autoxidation and thus exhibit prooxidant properties [82]. The prooxidant effect can be significantly enhanced by the reduction of Fe^{+3} into Fe^{+2} and the activation of Fenton reactions with the formation of reactive hydroxyl radicals. The prooxidant properties of some polyphenols are the basis of their cytotoxic and carcinogenic effects.

Intracellular ROS are important signaling molecules that control the functioning of a wide range of transcription factors and determine the profile of gene expression. Therefore, the prooxidant effect of polyphenols can positively affect the whole cell, inducing the synthesis of important antioxidant enzymes and preventing the realization of toxic effects ROS [6].

One of the proposed mechanisms of activation of the antioxidant system under the action of polyphenols involves the activation of the Keap1/Nrf2/ARE-pathway. The cytoplasmic protein Keap1 (Kelch-like ECH-associated protein 1) forms a complex with nuclear factor 2 (Nrf2), which regulates the activity of a number of genes responsible for antioxidant and anti-inflammatory effects. It is assumed that polyphenols affect both the phosphorylation of Keap 1 and the dissociation of the Nrf2-Keap 1 complex, causing the transport of Nrf2 to the nucleus, binding to ARE (the antioxidant response element), and induction of the corresponding genes [83]. In this process, an import-

ant role belongs to the extracellular signal-regulated kinase ERK1/2, protein kinases B and C, the activity of which, in turn, can also be regulated by various polyphenols: curcumin, resveratrol, epigallocatechin gallate, quercetin, apigenin, and viniferin [83]. The regulation of ε-protein kinase C by resveratrol and curcumin was shown [84]. ε-Protein kinase C plays an important role in protection against various stresses and diseases, such as ischemia, diabetes, and oncology. In addition, polyphenols can increase the Ca^{+2} level in the cytosol, alter the activity of many Ca^{+2}-dependent enzymes, affect energy metabolism and NO formation, which has a positive effect in cardiovascular diseases [78].

Recent studies have also shown that flavonoids can induce the synthesis of detoxifying enzymes—glutathione-S-transferase, NAD(P)H-quinone oxidoreductase, and UDP-glucuronosyltransferase—via possible interaction with regulatory sites of the EpRE genes (electrophile responsive element) [85].

The natural polyphenols present in food products, in particular, epigallocatechin gallate, gastrodine, gingerol, luteolin, resveratrol, theaflavin, and a number of others, can also affect different aspects of human health by modulating the microRNA level [86]. MicroRNA belongs to small noncoding RNAs (about 22 nucleotides) regulating gene expression at the post-translational level. It was suggested that plant flavonoids and stilbenes could modify the expression of microRNA and thus affect the expression of genes as a whole, which can potentiate their anti-inflammatory, anticarcinogenic, cardioprotective, and antiallergic actions [86].

Thus, a wide range of polyphenolic compounds is realized, both due to the manifestation of antioxidant/prooxidant properties that are more or less inherent to all these compounds and due to the specific interactions of polyphenols with different receptor and modulation of signaling pathways and their differentiated effect on transcription factors.

Biological effects of phytoalexins of flavonoid and stilbene natures in mammals. Many flavonoids and stilbenes in plants are present in the form of glycosides, which increases their solubility and makes them more readily available for absorption [87]. In the liver, phenolic compounds can undergo a number of transformations, including methylation, sulfatation, and glucuronidation, and break down to lower molecular weight compounds [6]. The polyphenol derivatives formed in the body can also exhibit biological activity [78].

An important point is the manifestation of antioxidant properties of phytoalexins in animals and humans in vivo [88–92]. For example, the plant *Ampelopsis grossedentata*, commonly known as "moyeam tea," was used in Chinese medicine for hundreds of years to treat hypertension, colds, fever, chronic arthritis, and other diseases [93–96]. The main biologically active component of this plant is dihydromyricetin (**DHM**), a natural flavonoid compound (2,3-dihydroflavonol). As an antioxidant, DHM inhibited lipid peroxidation and reduced ROS production in vitro [97, 98]. It was established that DHM protected endothelial cells from hydrogen peroxide induced oxidative stress by increased NO production and inhibition of ROS generation [99]. The antioxidant activity of DHM and its ability to chelate Fe^{2+} increased the viability of mesenchymal bone marrow stem cells (MSC) [100], which can be used for cell transplantation and tissue engineering.

Due to its antioxidant and anti-inflammatory properties, DHM prevented skin damage caused by UV radiation. The protective role of DHM against the UV-induced inflammatory response and apoptosis was demonstrated on the human keratinocyte cell line (HaCaT cells). The treatment of cells with DHM reduced the ROS production induced by UV radiation and prevented a decrease in the mitochondrial membrane potential and phosphorylation of the histone H2AX (γ-H2AX), a sensitive marker of DNA damage. In addition, DHM increased the activity of glutathione (**GSH**) reduction, reduced the malondialdehyde (**MDA**) content, and also prevented apoptosis in HaCaT cells subjected to UV irradiation. The antiapoptotic potential of DHM correlated with increased expression of antiapoptotic proteins (Bcl-2 and Bcl-xl) in the cells, reduced expression of proapoptotic proteins (Bax), and the inhibition of caspase activation. DHM also blocked the activation of the proinflammatory transcription factor NF-kB, playing a key role in the production of various proinflammatory cytokines and initiation of the inflammation reaction, and inhibited the phosphorylation of the N-terminal kinase (JNK), modulating NF-kB/p65 nuclear translocation [101]. These data expand the potential use of DHM as a prooxidant, proapoptotic and anti-inflammatory agent.

The antioxidant effect of DHM was used to normalize kidney function and reduce the nephrotoxicity induced by the antineoplastic agent cisplastin, which is used to treat bladder cancer, ovarian cancer, cervical cancer, lung carcinoma, and other types of cancers, and led to increased production of ROS and oxidative stress in cells and sections of the kidneys [99]. DHM reduced the MDA level, increased catalase and superoxide dismutase activities in mouse kidney tissues after treatment with cisplatin, and protected cells from cisplatin-induced inflammation and apoptotic death. A decrease in mRNA expression of some proinflammatory cytokines was also observed. The protective role of DHM was manifested not only in vitro but also in vivo, increasing the survival rate of animals [102].

DHM suppressed proliferation and induces apoptosis in tumor cells of hepatocellular carcinoma (HCC) of nine different lines but did not affect the growth of immortalized normal human liver cell lines [103]. DHM significantly reduced ROS production, GSH level, and the ATP generation in HepG2 cells, which

could disrupt redox reactions and induce apoptosis of tumor cells [104]. Thus, DHM has antitumor activity without obvious toxicity for normal cells. The antiproliferative and proapoptotic effects of DHM was demonstrated for other types of cancer. It was shown that DHM inhibited the proliferation of human gastric cancer cells (AGS cells) and induced cell apoptosis in a concentration-dependent manner. In addition, DHM regulates the expression of apoptotic genes, such as p53 and bcl-2. DHM caused an increase in p53 mRNA expression and inhibition of bcl-2 mRNA, which encodes the antiapoptotic Bcl-2 protein, without affecting the expression of Bax mRNA, which encodes the proapoptotic Bax protein [105]. The antitumor activity of DHM was also studied on thyroid cancer cells (HNSCC). It was demonstrated that DHM significantly induces apoptotic death and activates autophagy of HNSCC cells, as well as human melanoma tumor cells. In addition, it was established that autophagy could be a new mechanism by which cancer cells react to DHB [106]. The signal pathway of the nuclear factor kappaB (NF-kB B), a universal transcription factor regulating the expression of the immune response genes, apoptosis, and the cell cycle, was involved in autophagy induced by DHM. Moreover, N-acetylcysteine, which decreases the ROS level, stopped the effect of DHM on NF-kB-induced autophagy. These data indicate that the autophagy induced by DHM is associated with increased ROS production [107]. Thus, DHM is a natural compound that can be clinically effective for the treatment and prevention of tumors.

In recent years, a large number of studies have been devoted to other aspects of DHM action. Based on improvement of the carbohydrate and lipid metabolism in the liver, DHM was noted to have an "antialcohol" effect [108, 109]. It was also found that DHM could stimulate the secretion of irisin and myokine, which are activated in response to motor muscle activity. As a new exercise mimetic, DHM can be useful for patients suffering from metabolic diseases, as they cannot perform these exercises [110]. Along with this, DHM prevented the development of obesity, which was accompanied by a decrease in the proportion of skeletal muscles and insulin sensitivity, increasing the proportion of slow subcutaneous fibers and improving insulin resistance [111, 112]. DHM reduced the fasting glucose level and delayed the onset of glycaemia for 4 weeks in diabetic obese male rats. At the same time, DHM reduced weight gain and fat accumulation in the liver and in adipocytes. It was found that DHM has an antidiabetic effect by inhibiting phosphorylation of the serine residue 273 in the PPARɣ receptor involved in lipid and glucose metabolism [113]. It was concluded that DHM could be used for the prevention and treatment of insulin resistance and type 2 diabetes. DHM can also be used to prevent complications of diabetes, such as diabetic nephropathy and cardiomyopathy, which correlate with oxidative stress and inflammation response. Studies have shown that, due to its antioxidant and anti-inflammatory properties, DHM significantly improves the early stage of kidney damage in diabetic rats. The main mechanisms of this protective effect of DHM may be activation of the nuclear factor Nrf2, which is one of the important endogenous defense systems, and inhibition of the NF-kB signaling pathway, which regulates inflammatory and immune responses [114]. DHM also prevented diabetic cardiomyopathy in diabetic mice. The effect of DHM on the development of diabetic cardiopathy was associated with decreased oxidative stress and inflammation, improved mitochondrial function, inhibition of cardiac apoptosis, and restoration of cardiac autophagy. Treatment with DHM increased the activity of AMP-dependent protein kinase, which is decreased in diabetic mice. AMP-dependent protein kinase is the main regulator of energy homeostasis, controlling autophagy via phosphorylation and activation of ULK1 protein kinase (an autophagy marker) [115]. Thus, DHM may be a potential therapeutic agent for the early treatment of diabetic nephropathy and diabetic cardiopathy, although its mechanisms of action require further investigation.

At the moment, great attention is paid to the neuroprotective action of flavonoids. It was shown that flavonoids have neuroprotective effects on dopaminergic neurons. In particular, it was demonstrated that DHM reduced dopaminergic loss of neurons during Parkinson's disease [116, 117]. DHM improved the behavioral responses of animals with 3-nitropropionate-induced neuropathology [118]. It was found that DHM protects from cerebral ischemia, suppressing inflammation of microglial cells and releasing anti-inflammatory mediators, and significantly reduces the volume of infarction, microglia activation, and behavioral disorders after ischemic brain damage. DHM increased the viability of HT22 neuronal cells subjected to oxygen-glucose deprivation/reoxygenation, inhibited caspase 3, and activated the CRED transcription factor, Bcl-2, which increased the activity of protein kinases ERK1/2 and members of the family of mitogen-activated protein kinases regulating cell survival and apoptosis [119].

In the latest published review of Chinese scientists, the properties and various effects of DHM and the potential possibilities of its clinical application are discussed in detail [120]. However, a detailed analysis of the literature data accumulated to date demonstrated that, despite the large number of studies devoted to the biologically active effect of DHM, the mechanism of its action at the level of the cellular and subcellular structures is still not known.

Polyphenol of a stilbene nature resveratrol inhibited the processes of lipid peroxidation during intense physical activity and was accompanied by increased oxygen consumption and ROS generation. At the same time, resveratrol decreased lactate dehydroge-

nase and creatine kinase activities, the MDA level, and oxidative damage to DNA [121]. This polyphenol also reduced the MDA content in mononuclear blood cells and inhibited lipid peroxidation in platelets treated with peroxynitrite. Preincubation of smooth muscle aortic cells in cattle of with resveratrol prevented an increase in ROS production induced by oxidized low-density lipoproteins. Resveratrol reduced the ROS level in MCF-7 cells, inducing the expression of antioxidant genes, such as catalase and superoxide dismutase. Resveratrol also protected primary hepatocytes from oxidative stress by increasing the activity of catalase, Mn-dependent superoxide dismutase, glutathione peroxidase, NADPH, and glutathione-S-transferase and provided translocation of nuclear factor Nrf2 into the nucleus. Resveratrol activated the transcription of the antioxidant enzyme genes by binding to estrogen receptors, increased the activity of superoxide dismutase and glutathione peroxidase, and reduced the MDA level. Resveratrol prevented the development of aging due to its antioxidant properties [122].

In addition to the antioxidant effect, polyphenols can exhibit anti-inflammatory, antithrombotic, hepatoprotective, antiviral, and anticarcinogenic properties to different extents [123]. The anti-inflammatory effect manifested by resveratrol, which contributed to the protection of the vascular endothelium and reduced thrombosis, also improved blood supply in the osteonecrosis model [124]. Due to proapoptotic properties, resveratrol has advantages in the treatment of chronic inflammatory diseases characterized by the infiltration of neutrophils into inflamed tissues, such as rheumatoid arthritis and cystic fibrosis. In high concentrations, this polyphenol induced neutrophil apoptosis, which could help to relieve inflammation and stabilize tissue homeostasis [125]. Resveratrol significantly altered the production of cytokines and chemokines, regulating the acute inflammatory response in peripheral blood, endothelial cells, and macrophages, and regulated gene expression in various compartments of the systemic response to inflammation [126].

The cardioprotective action of resveratrol is also based on its antioxidant and anti-inflammatory properties. The regulation of resveratrol by endothelial NO synthase (eNOS) and the activation of NO synthesis in vivo, as well as its ability to trap ROS and retain lipid peroxidation, play an important role in these processes. An increase in NO synthesis under the action of resveratrol indicates the endothelioprotective (relaxing and protecting the vascular walls) properties of this compound [127]. The prevention of reperfusion rhythm disturbances due to the influence of resveratrol and, as a result, a reduction in the mortality rate were revealed by myocardial ischemia-reperfusion. The introduction of resveratrol decreased the number and duration of ventricular tachycardia and ventricular fibrillation and increased the NO content simultaneously with a decreased lactate dehydrogenase content in the blood of the carotid sinus [128].

Resveratrol is used for thrombovascular diseases, since it has anti-aggregative effect. It was found that the resveratrol effect is realized by inhibition of formation induced by NADPH oxidase and subsequent oxidative inactivation of the SHP-2-domain-containing protein tyrosine phosphatase 2 [129]. Evidence that resveratrol can directly protect cardiomyocytes upon diabetic cardiomyopathy were obtained. Resveratrol prevented glucose-induced apoptosis by suppressing the ROS generation by NADPH oxidase and maintaining endogenous antioxidant protection. These protective effects of resveratrol were associated with the functioning of AMP-dependent protein kinase [130]. A detailed description of the effect of resveratrol on various cardiovascular diseases is presented in the Bonnefont-Rousselot review, which discusses the possible mechanisms of resveratrol effects on atherosclerosis, hypertension, cerebrovascular accident, myocardial infarction, and cardiac decompensation and compares the results of preclinical studies with clinical trial data [131].

It was shown that the resveratrol dose dependently inhibits the proliferation and migration of human retinal epithelial cells (APRE-19) via the inhibition of APRE-19 cells in the S-phase without stimulation of apoptosis or inhibition of cells in the G1 or G2 phases. It was suggested that resveratrol might be useful in the treatment of proliferative vitreoretinopathy [132]. Resveratrol also inhibited the proliferation of fibroblasts of the pathological scar [133].

There is a clear association between obesity, inflammation, and diseases associated with obesity; therefore, the anti-inflammatory potential of resveratrol can directly affect other pathological conditions, such as obesity, diabetes, cardiovascular diseases, and neurodegeneration [134–136]. Animal studies demonstrated that resveratrol imitates the effects of caloric restriction by activating sirtuin 1 (SIRT1), an important regulator of homeostasis of cellular energy and mitochondrial biogenesis. Resveratrol influenced preadipocyte differentiation, preventing transmission of the insulin signal, mitochondrial biogenesis, lipogenesis, and lipid accumulation, which contributed to weight loss in humans and animals [137]. The effect of resveratrol on obesity was manifested at high polyphenol concentrations due to the induction of toxicity, whereas resveratrol at lower concentrations affected differentiation and lipolysis of preadipocytes [138]. Studies of the therapeutic effect of resveratrol on experimental diabetes demonstrated that polyphenol could have a beneficial effect on glucose homeostasis in obesity, diabetes, and metabolic dysfunction models. Resveratrol exhibited hypoglycemic and hypolipidemic effects and improved general symptoms of diabetes, such as polyphagia, polydipsia, and weight loss [139–141]. Preclinical studies have shown the positive

effect of resveratrol on the prevention and removal of metabolic disorders caused by obesity [136, 142].

3,5-Dihydroxy-trans-stilbene pinosylvin (**PS**), which shows a structural similarity with resveratrol, also has antioxidant, anti-inflammatory, antiproliferative, and chemoprotective properties and acts on many molecular targets [143]. The source of PS are the needles, core, and knots of pine wood of the family *Pinus*, as well as the vegetative part of *Gnetum cleistostachyum*. This phytoalexin is formed under environmental stress (fungal attack, UV light, ozone, drying). PS is a fungitoxin that protects the wood from fungal infection. However, unlike phytoalexins, which are synthesized during the infectious process, the PS is present in the plants before infection.

It was noted that the PS antioxidant properties are not inferior to the activity of dihydroquercetin, a key component of many commercial products based on polyphenols [144]. The limited existing data indicate that PS can be an inexpensive polyphenol that contributes to one's health by various methods. It was found that PS could protect the pigment epithelium of the retina, which plays a key role in maintaining normal vision, from death caused by oxidative stress. Treatment with PS at a concentration of 5–10 μM improved the survival of retinal cells under oxidative stress to 75–80%. In this case, PS induced the expression of hemoxygenase 1 (**HO-1**), a key inducible enzyme with cytoprotective, antioxidant, and anti-inflammatory effects. Inhibition of HO-1 can enhance ROS production, and HO-1 overexpression prevents the toxic effect caused by oxidative stress [145]. However, PS did not significantly affect the expression of the *Nrf2* gene, which acts as the transcription factor of antioxidant genes. Its protein products, including HO-1, are important for detoxification and elimination of reactive oxidants. In addition, PS did not affect the expression of the selective autophagy marker p62, which may indicate that p62 does not play a leading role in preventing oxidative stress, but it may be an important protein in cytoprotection during the late stage of oxidative stress and can induce adaptive autophagy [146]. A similar effect was obtained from the use of the willow bark extract, which protects endothelial cells of the human umbilical vein from oxidative stress by increasing the HO-1 level without altering the Nrf2 expression [147]. Thus, HO-1 is a target for the effects of PS and other flavonoids during protection of endothelial cells from oxidative stress and improvement of retinal survival. The study of the effect of PS on the activity of isolated human neutrophils showed that PS significantly reduced the formation of oxidants, both outside and inside the cell, and reduced ROS production. Inhibition of oxidant formation was not associated with a change in neutrophil viability, which did not decrease even with an increase in PS concentrations up to 100 μmol/L or with increased apoptosis. PS administration in rats with induced arthritis, in which the neutrophil count in the blood was sharply increased due to the action of proinflammatory cytokines on the neutrophilic activity of NADPH-oxidase, led to a decrease in the number of neutrophils and a significant decrease of ROS in the blood [148]. The antioxidant and anti-inflammatory effect of PS is the basis for potentiation of an immunosuppressant methotrexate on experimental arthritis. PS lowered the ROS concentration in the blood, the neutrophil count, and their phagocytic activity [149, 150]. The anti-inflammatory PS activity can be carried out by several mechanisms, such as a decrease in the synthesis of proinflammatory mediators and their release, and a decrease in the activity of immune cells, as well as suppression of the nuclear factor kB [151–154]. In addition, PS may decrease the expression of inducible NO synthase and NO formation, which converts into highly reactive peroxynitrite and activates proinflammatory signaling, contributing to the pathogenesis of arthritis. The anti-inflammatory properties of PS and monomethylpinosilvin were demonstrated by the model of mouse paw inflammation with an increased release of proinflammatory and regulatory mediators, including NO. PS and monomethylpinosilvin in micromolar concentrations reduced NO production and *iNOS* expression in activated macrophages and inhibited the production of inflammatory cytokines. This effect was comparable with the effect of the known inhibitor iNOSL-NIL [155]. Thus, PS is an effective inhibitor of neutrophil activity and can be used as an additional drug for conditions associated with persistent inflammation.

Like resveratrol, PS is a phenolic compound that can serve as a cardioprotective agent. Studies of the effects of PS on both proliferation and apoptosis of bovine aortic endothelial cells (BAECs) demonstrated that PS increases endothelial cell proliferation and has an antiapoptotic effect, which was associated with the inhibition of caspase-3. In addition, it was shown that PS activates endothelial NO synthase (eNOS) and promotes proliferation of endothelial cells by producing NO, since PS-induced cell proliferation was inhibited by treatment of the cells with an eNOS-L-NAME inhibitor. Another effect of PS was inhibition of lipopolysaccharide-induced adhesion of THP-1 cells (human monocyte cell line) to endothelial cells. The proliferative, migration, and adhesive activity of PS manifested at picomolar concentrations, whereas a similar effect of resveratrol was observed at nanomolar concentrations [156]. Thus, PS can be a promising phytotherapeutic agent for the prevention of cardiovascular inflammatory diseases, including ischemic pathologies, with an effectiveness higher than that of resveratrol.

Although PS induces cell proliferation, cell migration, and anti-inflammatory activity in endothelial cells at low concentrations (~pmol/L), PS at high concentrations (100 μM) induced the death of the endothelial cells of the cattle aorta. It was shown that a high PS concentration induced apoptosis of endo-

thelial cells by enhancing caspase-3 activity, nuclear fragmentation, and phosphatidylserine exposure but inhibited cell necrosis. PS induced the conversion of LC3 proteins associated with microtubules from LC3-I into LC3-II and degradation of p62, important autophagy indices. In addition, PS activated AMP-dependent protein kinase. It was also found that the inhibitor of autophagy stimulated the development of necrosis, and PS was then restored, whereas the caspase-3 inhibitor did not affect necrosis. These results show that PS-induced autophagy blocks necrotic progression in endothelial cells [157]. It was shown that stilbene compounds, including PS, induce dynamic autophagy, reduce protein aggregation, and prevent damage retinal pigment epithelium (RPE) during proteasome inhibition [158]. A high PS concentration promotes the activation of c-JunN-terminal kinase (JNK) and endothelial NO synthase (eNOS). It was found that SP-600125, a JNK inhibitor, inhibited PS-induced damage of endothelial cells, while L-NAME, an eNOS inhibitor, did not have any effect. This finding confirmed involvement of JNK in PS-induced apoptosis [159].

A number of publications demonstrated that PS has an anticarcinogenic effect. In studies of antiproliferative activity of PS on human colorectal cancer cells NST 116, PS was shown to inhibit proliferation of these cells by arresting the transition from G_1- into the S-phase of the cell cycle. In addition, PS induced the expression of the p21 and p53 proteins and suppressed expression of the transcription factor of c-Myc, which is involved in the transition of cells from G1 phase into S. PS also suppressed the nuclear translocation of β-catenin, which led to the suppression of β-catenin-mediated transcription of a number of target genes. All of these data indicate that the antiproliferative PS activity in colorectal cancer cells is associated with arrest of the cell cycle and suppression of the regulation of the signal pathways of cell proliferation [160]. It was found that PS methyl ester, which was isolated from green alder with a structure similar to that of resveratrol, is a potential inhibitor of prostate cancer cells (CRPCs). It was found that this new antiproliferative agent reduced the transmission of androgens and intracellular steroidogenesis, which was confirmed by decreased levels of AR and PSA proteins, as well as reduced expression of aldose-ketose reductase in CRPCs [161]. These results demonstrated the possible use of new approaches in the treatment of prostate cancer.

In addition to the anticarcinogenic effect, PS has an antimetastatic potential. The potential antimetastatic activity of PS was evaluated using in vitro and in vivo models. PS suppressed the expression of matrix metalloproteinase MMP-2, MMP-9 and membrane-type metalloproteinase in cultured human fibrosarcoma NT1080 cells. In addition, PS inhibited the migration of NT1080 cells and exhibited pronounced antimetastatic activity. In in vivo models of spontaneous pulmonary metastasis using colon cancer cells intravenously administered in mice, CT26 PS significantly inhibited the formation of tumor nodes and tumor mass in pulmonary tissues. The antimetastatic action of PS coincided with the decreased regulation of expression of MMP-9, cyclooxygenase-2 and decreased activity of ERK1/2 and Akt protein kinases [162]. These data suggest that PS can be an effective inhibitor of tumor cell metastasis via metalloproteinase modulation and can provide complementary PS action as a chemopreparative and antitumor agent. However, the data on the biological effects of PS are contradictory and do not provide the mechanism of action of this polyphenol at the molecular and cellular levels.

The natural flavonoid curcumin, which stimulates autophagy and antioxidant cell responses via regulation of extracellular and mitogen-dependent protein kinase signaling pathways in human leukemia HL-60 cells [6, 163], also possesses high pharmaceutical activity. A number of natural flavonoids have anticarcinogenic effects. Silibinin effectively suppresses MCF7 breast cancer cells via autophagy associated with mitochondrial dysfunction [164]. Wogonin and luteolin are also anticancer agents acting via autophagy amplification, while genistein, quercetin, and rottlerin induce apoptosis through canonical and noncanonical pathways, preventing tumor development and metastasis in vivo [6, 163]. Such flavonoids as silymarin, rutin, quercetin, and isoquercetin also possess hepatoprotective properties, and naringin, baicalin, and apigenin are neuroprotective compounds [6, 163]. In total, about 20 flavonoids with a wide range of positive effects on human health and of great medical interest are at the stage of entry into the market [163].

POLYPHENOL PRODUCTION IN MICROBIAL BIOTECHNOLOGY

The possibility of using biologically active polyphenols dictates the need to obtain industrially significant volumes of these compounds. However, since the phytoalexin content in plants is low, their isolation through sequential extraction with subsequent purification not only requires large quantities of plant raw materials but also determines the long duration, energy intensity, and high cost of the products. Therefore, metabolic engineering methods for the synthesis of biologically active polyphenols becomes increasingly important [165, 166].

It is known that flavonoids are produced by all land plants during the metabolism of phenylpropanoids. Phenylpropanoids are the source of a number of interrelated flavonoid structures forming the nine major subgroups: chalcones, aurones, isoflavones, flavones, flavonols, flavandioles, anthocyanins, tannins, and phlobaphene pigments. Chalcone, which formed in the first stage of synthesis via the condensation of malonyl-CoA and 4-coumaryl CoA in the chalcone synthase reaction, is a precursor of a significant number of flavonoids (Fig. 2). Under the action of chalcone,

isomerase chalcones converted into flavonones, which in turn, can be converted into compounds of other subclasses via modification of the flavonoid skeleton (see Fig. 2).

During genetic manipulations that make it possible to reproduce complex pathways for the biosynthesis of flavonoid compounds in producer microorganisms, the following must be considered: (1) flavonoid components usually accumulate in certain tissues or plant organs (for example, in the fruit skin); (2) the synthesis of certain compounds is clearly species-related; and (3) the production of phytoalexins and their biological activity are finely regulated during plant differentiation and depend on environmental conditions [166]. The flavonoid-producing organism must have the ability to synthesize a core molecule, for example, flavanone naringenin, which can then be converted to other compounds of a flavonoid nature. Among the potential producers, various microorganisms have been proposed—*Escherichia coli, Saccharomyces cerevisiae, Streptomyces venezuelae,* and *Phellinus signarius*. The enzymatic production of flavonoids by the constructed phenylpropanoid pathway in *E. coli* was the first example demonstrating the possibility of functioning of the full pathway for the biosynthesis of flavonones from amino acid precursors in heterologous microorganisms [167]. Leonard et al. [168], using the transformed *E. coli* culture, demonstrated a conversion of p-cinnamic acid, phenylalanine, and tyrosine into pinocembrin, naringenin, and eriodictyol with a yield of 429 mg per liter, while *S. cerevisiae* transformants under similar conditions showed a smaller titer of the final products, 8.9 mg per liter [169]. It is interesting to note that a number of studies demonstrated the high productivity of pinocembrin and naringenin during glucose utilization without the use of amino acid precursors: 40 mg per liter with the *E. coli* system [170] and 108.9 mg per liter for the yeast producer [171]. Optimization of the product yield was carried out in the first case due to the use of genes encoding enzymes insensitive to an increase in the intracellular phenylalanine pool. In the second case, the authors applied a similar strategy, inducing the suppression of the feedback inhibition of 3-deoxy-D-arabinose-heptulosonate-7-phosphate synthase (*Aro3, Aro4*) and thereby increasing the pool of aromatic amino acid precursors. In addition, the expressions of chalcone synthase and heterologous tyrosine-ammonia lyase were increased, which, together with variation of the pH of the cultivation medium, increased the efficiency of flavonoid synthesis by 40 times.

Microbial producers demonstrated high efficiency also in the biosynthesis of flavones and flavonols, requiring the involvement of two additional enzymes in the synthesis, flavone synthase 1 and flavonol synthase, which catalyze the oxidation of the corresponding substrates with the formation of C_2–C_3 double bonds (Fig. 2). Flavones apigenin and chrysin were synthesized in *E. coli* in a yield of 13 and 9.4 mg per 1 L [172]. Flavonol synthase cloned from ginkgo (*Ginkgo biloba*) [173] and mandarin (*Citrus unshiu*) [174] was effective in the transformation of *E. coli*, ensuring the conversion of the flavone naringenin into kaempferol. The complete synthesis of kaempferol from phenylalanine at a high level of malonyl-CoA was also obtained in *S. cerevisiae* [175]. However, it was not possible to obtain flavonols during glucose utilization by producers without precursors.

The production of heterologous isoflavonones with the use of isoflavone synthase cloned from soybean (*Glicine max*) in the *E. coli* and *S. cerevisiae* expression systems was successful [176]. Transas et al. [169] reconstructed the full pathway of genistein production, including seven genes under the control of the *GAL* promoter. This pathway in the presence of phenylalanine provided 0.1 mg of isoflavonone per L.

Methodological techniques are used to optimize flavonoid production. They include a combination of promoters and target genes, knockouts of the accompanying genes, in particular, the gene encoding UDP-glucose dehydrogenase producing UDP-glucose, which in turn prevents the effective flavonoid synthesis, increased malonyl-CoA level by overexpression of acetyl-CoA carboxylase from the enterobacteria *Photorhabdus luminescens*, and the construction of artificial enzymes of P450 cytochrome system [176].

Active development of the artificial production of biologically active stilbenes is also performed. For example, resveratrol, the most popular stilbene in the field of medicine, which is synthesized in nature from one molecule of coumaroyl-CoA and 3 molecules of malonyl-CoA by stilbene synthase, was obtained in a 7.5-fold amount due to overexpression of the gene of this enzyme (*Vst1*) in transformed grape plants (*Vitis venifera*) [177]. The production of resveratrol in grape-cell suspension culture by the addition of methylated β-dextrin as an elicitor was also successful [178]. In this case, the authors obtained 5.207 g of trans-resveratrol in 1 L, while its content in grape skins under native conditions does not exceed 1.5–7.8 mg per 1 g of fresh weight [179]. Heterologous microorganisms *E. coli* and *S. cerevisiae* were also used for resveratrol production. Yeast host organisms proved to be preferable due to their high resistance to low pH and osmotic stress, food safety, and the presence in the genome of certain genes, in particular, cinnamate-4-hydroxylase (*C4H*), which catalyzes the second stage of phenylpropanoid pathway. A high resveratrol yield in transformed yeast cells—531.41 mg per 1 L—as obtained by metabolic engineering [180]. Another approach to stilbene production, which consisted of the use of amino acid precursors, was used recently, resulting in the use of the wild-strain *Alternaria sp*. MG1. This approach made it possible to obtain1.376 mg of resveratrol from 1 L of phenylalanine [181].

The pptimization of stilbene production in microbial biotechnologies includes the use of whole com-

plexes of metabolic pathways, including a block of several genes performing the biosynthesis of stilbene polyphenols and the use of elicitors activating the protective mechanisms of plants and thus increasing the expression and synthesis of phytoalexins and the use of exogenous genes, for example, the *rolB* agrobacterial gene, which increased resveratrol synthesis by 100 times [182].

Thus, the advances made in the field of metabolic engineering of flavonoids and stilbenes suggest that these compounds are extremely promising agents in the development and testing of new effective drugs.

CONCLUSIONS

Flavonoids and stilbenes are secondary plant metabolites that have a unique ability to control and modulate key intracellular processes: growth and differentiation, ROS production, enzyme induction, the development of inflammation, apoptosis, and signal transduction, the functioning of ion channels and neurotransmitters, and gene transcription. Polyphenolic antioxidants are powerful cellular protectors in various inflammatory processes, cardiovascular pathologies, pathologies associated with obesity, diabetes, neurological disorders, almost all known types of cancer, and bacterial, viral, and fungal infections that are multiresistant to the majority of antibiotics. A large number of studies demonstrated that phytoalexins of flavonoid and stilbene natures activate antioxidant cellular pathways, modulate the immune response by inhibiting anti-inflammatory biomarkers, induce antioxidant enzymes and chelate metals, modulate autophagy and prion proteins, and inhibit/induce apoptotic cell death in various pathology models, preventing the development of various types of cancer.

Approaches to the metabolic engineering of economically significant compounds of a flavonoid nature that have been developed in recent decades give grounds to consider them extremely promising natural compounds that exhibit high efficiency in the vast majority of models of severe pathologies of plants, animals, and humans. Clinical trials show that natural polyphenols are absorbed well by the human body and have practically no toxic side effects; they beneficially influence the biomarkers of a number of diseases. However, for a full understanding the therapeutic potential of polyphenols, it is necessary to have more clinical evidence that will allow the compilation of a complete picture of their pharmacological potential.

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