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Chemical Features of Medicinal Plants (Review)

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Abstract—Data on chemical composition related to the synthesis of physiologically active substances (alkaloids, terpenoids, glycosides, phenolic compounds, etc.) and to the accumulation of individual elements or groups of five to ten elements (e.g., Cr, Co, Mn, and Zn) in medicinal plants were reviewed. Chemical features of medicinal plants serve as an integral determinant of their species specificity and pharmacological properties and enable their wide use in medical practice. The relationship between the synthesis of physiologically active substances and accumulation of elements is mediated by several levels of molecular regulation.

Medicinal plants produce marked therapeutic effects on the human body. They have been used for many years. Currently, interest in medicinal plants is increasing. In Russia, there are more than 200 species of medicinal plants belonging to various taxonomic groups. The majority of them are flowering plants of more than 80 families, including *Solanaceae*, *Asteraceae*, *Rosaceae*, *Leguminosae*, *Papaveraceae*, and *Lamiaceae* [1–3]. Some specimens of gymnosperms (Scotch pine, *Pinus sylvestris* L.), horsetails (*Equisetum arvense* L.), and algae (sea cabbage, *Laminaria jaronica Aresch*.) are medicinal plants.

Medicinal plants display diverse pharmacological activities (e.g., antimicrobial, adaptive, stimulatory, and sedative properties). They are used as cholagogic, hypotensive, capillary-enforcing, antiulcer, anticholinesterase, anticancer, spasmolytic, analgesic, and analeptic medications [1–4]. An advantage of medicinal plants is that they provide patients with a complex of natural compounds, have smoother action and are better tolerated than synthetic drugs, and produce few allergic reactions. They do not accumulated and therefore can be administered for a long time. Medicinal plants and phytopreparations are used for therapy and prevention of various human diseases, including cardiovascular, gastrointestinal, nervous, and skin diseases, and even malignancies [2, 3, 5].

Here, we review data on the chemical composition, synthesis of physiologically active substances (PAS), and accumulation of individual elements in medicinal plants and correlate their pharmacological properties with chemical peculiarities.

1. PHYSIOLOGICALLY ACTIVE SUBSTANCES

Therapeutic effects of medicinal plants were shown to be associated with their chemical peculiarities. As differentiated from other plants, medicinal plants synthesize and accumulate natural PAS with marked physiological activities. Alkaloids, terpenoids (triterpene and steroid saponins), phenolic compounds, glycosides (cardiac glycosides), and polysaccharides are of particular interest in respect to their therapeutic effects [3]. Each class of these PAS comprises various structural types.

Alkaloids. Depending on the structures of their heterocycles, alkaloids are derivatives of pyrrolidine, pyridine, piperidine, quinoline, isoquinoline, indole, tropane, quinolizidine, purine, etc. Alkaloids are represented by simple, complex, or even high-molecular-weight polycyclic compounds. There are more than 10 000 known alkaloids [6, 7].

Phenolic compounds. Phenolic compounds of various chemical compositions are abundant in plants. They comprise C_6 (the simplest phenolic compounds), C_6–C_1 (hydroxybenzoic acids and their derivatives), C_6–C_3 (phenylpropanoids, hydroxycinnamic acids, umbelliferone, and lignans), C_6–C_3–C_6 (flavonoids, including flavanones, flavones, flavonols, catechols, leucoanthocyanidins, anthocyanins, anthraquinones, etc.), and polymeric phenolic compounds (tanning agents) [8]. Medicinal plants contain various amounts of phenolic compounds, the active ingredients that determine the therapeutic effects of many plants. Even in medicinal plants whose effects are related to other types of PAS, phenolic compounds determine the specific properties that differ from those of synthetic drugs with the same therapeutic effects [3].

Terpenoids. Terpenoids is a major class of PAS consisting of more than 10 000 compounds that also determine the pharmacological activity of medicinal plants. Depending on the number of isoprenoid groups (C_5H_3), terpenoids are divided into monoterpenes, sesquiterpenes, diterpenes, tetraterpenes, and polyterpenes. These compounds have various applications. Some polyterpenes are auxiliary component constituents (rubber and

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gutta-percha). Diterpenes and tetraterpenes represented by vitamins and provitamins are major components of food products, not only medicinal compounds. Triterpenes play the role of aglycones (sapogenins) in the composition of triterpene saponins and are widely used in medical practice [9].

Triterpene saponins. Triterpene saponins are derivatives of cycloartane, dammarane, α-amirin, β-amirin, and other compounds. Dammarane derivatives include the saponins of ginseng (*Panax ginseng* C. A. Mey). β-Amirin derivatives are represented by saponins of licorice (*Glycyrrhiza glabra* L.), which are used in Chinese and Tibetan medical practices. Beginning from Homer's time, licorice was mentioned in many European medical texts [10]. A search through computer databases showed that licorice is the most widely used plant in medical practice, leading both ginseng and *Rhodiola rosea* L. [3]. The pharmacological activities of saponin-containing medicinal plants result in their marked therapeutic effects. Saponins of calendula (*Calendula officinalis* L.), locoweed (*Astragalus dasuantus* Pall.), Jacob's ladder (*Polemonium coeruleum* L.), horse chestnut (*Aesculus hippocastanum* L.), and licorice (*Glycyrrhiza glabra*) display antiarrhythmic, sedative, analgesic, antiinflammatory, expectorant, diuretic, cardiotonic, and capillary-enforcing activities. These plants are used for therapy in upper respiratory tract disorders (licorice and Jacob's ladder), hypertension (locoweed), venous insufficiency (horse chestnut), and disturbances in salt-water metabolism (licorice) [1–3].

Steroid saponins. Steroid saponins are of considerable medical importance. Diosgenin (a steroid sapogenin) plays the role of an aglycone in these compounds [11]. Diosgenin isolated from roots of *Dioscorea deltoidea* Wall or *Dioscorea nipponica* Makino is the major raw material for hormonal drugs (cortisone, hydrocortisone, prednisolone, prednisone, etc.) and polysponin (*Dioscorea nipponica* Makino). Hormonal preparations are widely used for treating Addison's disease, arthritis, tendovaginitis, blepharitis, keratitis, and iritis, as well as viral and fungal diseases [12]. Polysponin is used for treating atherosclerosis. Currently, the demands for diosgenin are hundreds of thousands of metric tons per year. Therefore, the search for new sources of plant steroids (such as laciniate nightshade, *Solanum laciniatum* Ait.) is an urgent problem.

Essential oils. Plants containing essential oils, as well as the pure essential oils isolated from these plants, are important in medical practice. Essential oils are complex multicomponent mixtures of fragrant volatile substances, monoterpenes, sesquiterpenes, aromatic compounds, and their derivatives. An essential oil may contain hundreds of components, some of which are formed during industrial processing (synthetic components). Essential oils produce astringent, bactericidal, and antiinflammatory effects. These oils are isolated from sage (*Salvia officinalis* L.), certain eucalyptus species (such as *Eucalyptus cinerea* F. Muell. ex Benth.), peppermint (*Mentha piperita* L.), and Scotch pine. Essential oils obtained from elecampane (*Inula helenium* L.) and linden (*Tilia cordata* Mill) are used as expectorants and diaphoretics, respectively. Some essential oils (e.g., those obtained from garden heliotrope, *Valeriana officinalis* L.) have sedative effects.

Glycosides. Medicinal plants were shown to contain glycosides. Depending on the nature of their aglycones, glycosides are divided into cardiac glycosides, anthraglycosides, iridoids (bitter glycosides), cyanogenic glycosides, thioglycosides, and isothiocyanates. Cardiac glycosides display the highest therapeutic activity. There are no synthetic substitutes for cardiac glycosides; medicinal plants are the sole source of these substances. Cardiac glycosides induce strong specific effects on the myocardium and enhance the strength of cardiac contractions. Aglycones of cardiac glycosides are derivatives of cyclopentanoperhydrophenanthrene containing five- and six-membered lactone rings as substituents. The effects of these substances on the myocardium are related to the presence of these five- and six-membered lactone rings (in cardenolides and bufadienolides, respectively) localized at the C-17 position of aglycones. Their degradation leads to a complete loss of cardiac effects.

Other aglycone substitutes (methyl and hydroxyl groups), as well as their number and localization, determine pharmacological properties of glycosides, e.g., the rate of elimination and the degree of accumulation in the body (even at toxic concentrations), especially during long-term treatment. The sugar fragment of cardiac glycosides also contributes to their pharmacological effects. Because this fragment is unstable, fermentation of plant materials should be conducted under optimum conditions to preserve the native state of cardiac glycosides.

Polysaccharides. Pectins, resins, and mucilages are the major polysaccharides used in medical practice. Pectins serve as emulsifiers and stabilizers, constitute the main components of ointments with salicylic and boric acids, and enter the composition of drugs decreasing blood cholesterol content and modulating bile acid metabolism. Resins are used for the production of oil emulsions, mucilaginous solutions, and blood substitute liquids. Aqueous and mucilaginous extracts prepared from mucilage-containing plants, flax (*Linum usitatissimum* L.) and marsh mallow (*Althaea officinalis* L.), are used to treat catarrhs and gastrointestinal tract lesions and to counteract the irritant effects of other drugs.

Thus, the therapeutic effect of medicinal plants is related to the presence of alkaloids, terpenoids, glycosides, phenolic compounds, polysaccharides, and other components whose synthesis is characteristic of these species. The above list of PAS is far from being full and contains the substances most important in this respect. It should be emphasized that medicinal plants contain

complexes of various classes of PAS, which determines the diversity of their therapeutic effects on the body.

2. SPECIFICITY OF ELEMENTAL COMPOSITION

The specificity of the chemical properties of medicinal plants is not restricted to the synthesis of PAS. Medicinal plants accumulate individual elements or groups of elements at concentrations much higher than their average content in plants of the same origin (Clarke's value, C) [3, 13]. Measurements of the contents of four macroelements and 20 microelements in more than 200 species of medicinal plants showed that the majority of these plants (≈90%) accumulate these elements to different extents [3]. There are moderate concentrators (2 C), concentrators (2–9 C), and overconcentrators of elements. In overconcentrators (20–56% of PAS-synthesizing plants), the content of elements is more than one order of magnitude higher than the C value.

Medicinal plants accumulate biologically important elements (Cr, Mn, Fe, Cu, Co, Se, and Zn), halogens (J and Br), and precious metals (Au and Ag). The contents of these elements in various plants are different. Most medicinal plants accumulate groups of five to ten biologically important elements (primarily Cr). According to the classification of Perel'man, Cr is an element with a low degree of accumulation by higher plants [14]. This property of Cr and the excessive refinement of food products lead to Cr deficiency in humans. It was shown that half of America (in particular, elderly and aged people) suffers from Cr deficiency, which leads to cardiovascular disorders, atherosclerosis, endocrine diseases, hyperglycemia, encephalopathy, peripheral neuropathy, and diabetes mellitus. Cr (in addition to insulin) regulates blood sugar concentration [3, 15–17].

The fact that medicinal plants (124 of 196 species studied) are concentrators (3–10 C) or overconcentrators (37–114 C) of Cr is of considerable importance. Various food products, carrot (*Daucus sativus* (Hoffm.) Roehl.), onion (*Allium victorialis*), corn (*Zea majus* L.), black currant (*Ribes nigrum* L.), and dog rose (*Rosa majalis* Herrm.), as well as herbs line parsley (*Petroselinum crispum* (Mill.) A. W. Hill), dill (*Anrthum graveolens* L.), laurel (*Laurus nobilis* L.), and caraway (*Carum carvi* L.), are concentrators or overconcentrators of Cr. Some of these plants, garden heliotrope (*Valeriana officinalis* L.), motherwort (*Leonurus cardiaca* L.), hawthorn (*Crataegus sanguinea* Pall.), chamomile (*Chamamilla recutita* L.), peppermint (*Mentha piperita* L.), and pansy (*Viola trocolor* L.), are widely used as medicines [3, 17]. The daily dose of Cr consumption varies from 50 to 200 μg. Therefore, medicinal plants can prevent Cr deficiency and cover the demands for this element [3, 17].

In addition to Cr, medicinal plants accumulate Se. It was shown that 112 of 196 plant species studied are concentrators of Se. One species (Urals licorice, *C. uralensis* Fisch.) was shown to be an overconcentrator of Cr (11 C). Specimens of the family *Leguminosae* are the most active in accumulating Se from soil [18]. The absolute amount of Se in Se-accumulating plants is only two to eight times higher than the C value. On the other hand, the content of Se in sod–podzolic soils of non-chernozem Russian regions is extremely small [19].

The coefficient of biological accumulation (CBA) is a good criterion reflecting the ability of medicinal plants to accumulate Se. Plant species are considered concentrators if CBA (the ratio between element content in plants and its concentration in the soil) is equal or slightly higher than 1. In medicinal plants, CBA varies from 20 to 70. Therefore, the ability of medicinal plants to accumulate Se is only partially realized. Probably, the use of Se-containing microfertilizers will allow us to markedly increase the content of Se in plants (even to overdoses). In this case, the number of plants over-concentrating Se will also increase.

A low content of Se in the soil of nearly all Russian regions leads to its deficiency in the whole soil–plant–animal–human system (with delayed and progressive manifestations). Se imbalance causes severe diseases, such as malignant tumors, atherosclerosis, cardiomyopathy, arrhythmia, fibrillation, and allergic diathesis [20]. A low content of Se in the blood and urine is the main diagnostic criterion for some diseases. Plants concentrating Se hold much promise for the prevention of Se deficiency. Medicinal plants enhance the assimilability of Se in the organically bound form and can be used for a long time. Plants contain Se in the form of free Se-containing amino acids (selenomethionine and selenocysteine) or complexes with proteins [18].

In addition to Cr and Se, many medicinal plants concentrate Fe, Mn, Co, Zn, and Cu, which modulate the metabolism of PAS and whose roles are considered in more detail in a special section of this paper. These plants also accumulate halogens and precious metals, some of which are worth noting. Alder (*Alnus incana* (L.) Moench.) is a unique overconcentrator of J (340 C) [3].

It was demonstrated that approximately 7% of medicinal plants accumulate Ag. Lily of the valley (*Convallaria majalis* L.), common foxglove (*Digitalis purpurea* L.), ginseng, and arnica (*Aronia melanocarpa* (Michx.) Elliot.) are used as medicines. Cowberry (*Vaccinium vitis-idaea* L.) and dill are used as food products and seasoners, respectively. Wallflower (*Erysimum diffusum* Ehrh.) is the sole concentrator of Au. Since the contents of Ag and Au in the soils of their natural habitats are extremely small, their selective absorption and accumulation seem to be surprising, confirm the specific elemental composition of medicinal plants, and have much importance. Precious metals having therapeutic properties are used for treating allergic diathesis (H. Picard's classification [21]).

In addition to biologically important elements, some medicinal plants accumulate toxic heavy metals, Pb and Cd, at high concentrations. Blueberry (*Vaccinum myrtillus* L.) and May apple (*Podophyllum emodi*

Wall.) are overconcentrators of Pb (16 C and 64 C, respectively). Cudweed (*Gnaphalium uliginosum* L.) is an overconcentrator of Cd (15 C) [22]. Taking into account species peculiarities of medicinal plants and marked environmental contamination, these plants should be gathered at a distance from roads and industrial enterprises.

Thus, the majority of medicinal plants can concentrate individual elements or groups of five to ten elements. No correlation was found between the elemental composition of medicinal plants and the type of PAS. However, there were strong interrelations between the quantitative characteristics of element accumulation. This refers to the absolute content of elements in plants and the quantitative ratio between them, which vary due to the ability of plants to synthesize different PAS [22–26].

The degree of dispersion decreases and the coefficient of correlation between elements concentrated increases with the transition from plants synthesizing alkaloids of various types to plants producing only individual alkaloids (derivatives of tropane and isoquinoline and biogenetically similar diterpene and steroid alkaloids having the same precursor, mevalonic acid). However, there are some variations in these quantitative characteristics. The degree of dispersion decreases two- to eight-fold and the number of pairs with high correlation coefficients increases (0.56–0.97; Fe, Al, and Cr; and Mn, Ba, and Zn) in tropane-producing plants compared to those in plants synthesizing alkaloids of various types.

The degree of dispersion tends to decrease in plants synthesizing isoquinolines and alkaloids having mevalonic acid as a precursor. A decrease in the degree of dispersion is accompanied by an increase in the number of pairs with high correlation coefficients (0.56–0.97). The number of such pairs (Fe, Mn, Cu, Zn, Co, Cr, Al, Ba, and B) increases to 14 (isoquinolines) and 11 (diterpenes and steroid alkaloids). Thus, medicinal plants display the ability to accumulate elements in various quantitative ratios, which correlates with the type of PAS synthesized [25, 26].

3. REGULATION OF PAS METABOLISM: MOLECULAR LEVELS AND THE ROLE OF METALS

The mechanisms underlying molecular regulation of PAS metabolism (primary precursors, assimilability, active transport, activation or inhibition of enzymes catalyzing biosynthesis, and compartmentalization) are of considerable interest [27–30]. Compartmentalization is realized at the organism (hole plant), organ, tissue, cellular, and subcellular levels, which provides the spatial independence of various metabolic stages, as well as the conditions necessary for PAS isolation and accumulation. Metals playing the role of cofactors or activators of enzymes, which catalyze various stages of natural compound metabolism, can modulate these processes.

Metals which are most often concentrated by medicinal plants that synthesize and accumulate PAS of various types (alkaloids, phenolic compounds, terpenoids, etc.) play the role of cofactors or activators of enzymes. Such metals (Co, Zn, Fe, Cu, Mn, and Cr) display their activity at various molecular levels. The effects of Co and Zn are realized by supplying primary precursors at the very early stages of PAS biosynthesis. These PAS having aromatic amino acids (phenylalanine, tyrosine, and tryptophan) as primary precursors [6, 31] comprise the majority of alkaloids, derivatives of tropane, isoquinoline, and indole, and nearly all phenolic compounds independent of the structure and composition of their molecules [6–8].

Co and Zn act as activators of key enzymes catalyzing the biosynthesis of aromatic amino acids by the shikimate pathway. Co-dependent enzymes include cytosolic isoenzyme 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP) synthase [32, 33] and 3-dehydroquinate synthase [34]. Tryptophan synthase is a Zn-dependent enzyme [35]. Co-dependent enzymes catalyze the formation of DAHP and 3-dehydroquinic acid that act as primary precursors of phenolic compounds and, therefore, play a key role in their biosynthesis [32–34]. Structural fragments of alkaloids are formed from tyrosine, phenylalanine, and tryptophan [6, 7, 31].

In addition to Co and Zn, Mn ions modulate the initial stages of phenolic compound biosynthesis. DAHP synthase (Mn-dependent plastid isoenzyme) is involved in the biosynthesis of phenolic compounds by the shikimate pathway [8]. Mn ions activate phenylalanine ammonia-lyase (PAL, EC 4.3.1.5), catalyzing the deamination of phenylalanine with the formation of *trans*-cinnamic acid [36]. This is a key reaction in the biosynthesis of phenolic compounds. Assimilation products of the shikimate pathway undergo biotransformation through this reaction with the formation of natural compounds. The PAL-catalyzed reaction is an intermediate stage between the primary and secondary metabolic processes, because not only phenolic compounds but also cyanogenic glycosides, phenol components of essential oils, phenol alkaloids, and anthracene derivatives are formed from phenylalanine [8].

Mn ions activate carboxylase and, therefore, affect the biosynthesis of alkaloids. Carboxylation (in addition to decarboxylation) is the major step of alkaloid formation from primary precursors [6, 7]. 3-Dehydroquinic acid, the first cyclic metabolite containing the benzene ring (the major structural fragment of phenols), plays a key role at the initial stages of phenolic compound biosynthesis [8]. 3-Dehydroquinate synthase catalyzing 3-dehydroquinic acid formation requires the presence of Cu ions [37–39].

Thus, Co, Zn, Mn, and Cu affect the initial stage of PAS biosynthesis. These ions, as well as Fe, act as cofactors or activators of enzymes catalyzing PAS

metabolism, which yields natural compounds of various types. These reactions include PAS biosynthesis from primary precursors, their transformations, and resynthesis from intermediate metabolites formed after *in situ* conversion of PAS. It is difficult to differentiate the formation and conversion of complex multicomponent PAS, because the final step of biosynthesis of one compound can be the initial stage of its transformation or synthesis a similar metabolite [6, 7].

Fe ions act as cofactors or activators of enzymes catalyzing biosynthesis, transformation, and resynthesis of compounds in medicinal plants with phenol type metabolism. Fe ions activate and stabilize flavone synthase 1 and flavone-3-hydroxylase catalyzing oxidative conversions of flavanone into flavone and dihydroflavonol, respectively [40, 41]. Since these enzymes are extremely unstable, the stabilizing effect of Fe is important. In addition to this, the flavonol synthase catalyzing conversion of dihydrokaempferol and dihydroquercetin into kaempferol and quercetin, respectively, requires the presence of Fe ions [42]. Thus, Fe ions play an important role in the formation of various flavonoids.

Fe ions serve as cofactors of peroxidase, the polyfunctional enzyme with wide substrate specificity that oxidizes phenolic compounds. Peroxidase catalyzes hydrolysis, oxidation (including peroxidase cleavage), and disintegration of flavonol, as well as transformation and resynthesis of other enzymes [43].

Cu ions are also involved in the biosynthesis of phenolic compounds. These ions act as cofactors of phenol oxidase, which catalyzes the conversion of *p*-coumaric acid into caffeic acid and the hydroxylation of the B ring at the C-3^1 position of flavonoids (kaempferol and naringenin and etc.) [44–46]. Cu ions are cofactors of polyphenol oxidase (tyrosinase). Tyrosinase, glycosidases, and peroxidase cleave phenols and, therefore, are involved in their metabolism (see the description of peroxidase) [43].

Most phenolic compounds are formed from *trans*-cinnamic acid, which plays the central role in their metabolism. *p*-Hydroxylation of *trans*-cinnamic acid catalyzed by Mn-dependent *trans*-cinnamic acid 4-hydroxylase results in the formation of *p*-hydroxycinnamic (*p*-coumaric) acid [47]. Mn ions are necessary for specific transferases catalyzing O- and C-glycosylation of hydroxycinnamic acids, flavonoids, and other compounds with the formation of their derivatives. The yield of these reactions depends on the nature, number, and localization of sugar residues [48]. Mn ions activate arginase and stimulate the formation of alkaloids containing the pyrrolidine heterocycle. These alkaloids include derivatives of pyrrolidine, pyrrolizidine, and tropane (nicotine and its analogues, stachydrine, hygrine, coushygrine, hyoscyamine and its analogues, and retronecine) [6, 7].

Co and Zn stimulate alkaloid synthesis in medicinal plants. Co ions modulate the formation of tropanes by stimulating isomerization of the lateral chain in phenylalanine (intramolecular rearrangement). This reaction results in transformation of phenylalanine into tropic acid, the main structural fragment of alkaloids [49]. Co ions are also involved in the metabolism of folic acid. This substance plays the major role in primary methylation and transmethylation, which involve one-carbon residues and betaine, respectively [6, 7]. These processes result in methylation and demethylation of alkaloids with the formation of O-methyl and N-methyl, the major functional groups in their molecules [6, 7, 31]. Zn ions stimulate the incorporation of tryptophan (primary indole precursor) into vindoline, the major alkaloid of *Catharanthus roseus* (l.) G. Don. containing more than 90 alkaloid compounds [49].

Cr ions concentrated by 90% of medicinal plants are also involved in the metabolism of PAS. Cr ions inhibit nonspecific phosphatases that catalyze cleavage of phosphorylated intermediates, phosphoric acid esters and other energy-rich compounds formed during PAS biosynthesis. This Cr-induced stabilization of intermediates promotes their intensive biosynthesis [17].

The effects of Cr on lupanine alkaloid formation are realized not only via phosphorus metabolism. Cr ions inhibit one of the major reactions in lupanine alkaloid metabolism, acylation of 13-hydroxylupanine yielding 13-hydroxylupanine esters. Cr ions decrease the content of esters, which leads to an increase in the concentrations of their primary precursors, lupanine and 13-hydroxylupanine [17, 50, 51]. The inhibitory effect of Cr on 13-hydroxylupanine acylation is consistent with the high affinity of these ions for SH groups, which play an important role in CoA-mediated acylation of various substrates [52].

Thus, metals concentrated by medicinal plants act as cofactors or activators of enzymes involved in PAS metabolism. Metals modulate the synthesis, transformation, and accumulation of PAS by activating or inhibiting these enzymes. The effects of metals can be mediated via various stages of basal metabolism. In this case, their influences are enhanced. Cu ions are involved in nitrogen metabolism and activate the synthesis of nitrogen-containing compounds, including aromatic amino acids [53]. Since aromatic amino acids serve as primary precursors of alkaloid PAS and phenolic compounds, Cu ions provide the optimal conditions for their formation.

Zn ions affect the metabolism of indole alkaloids by stimulating the formation of indolylacetic acid (IAA), which in turn activates their synthesis [54]. Zn ions not only activate tryptophan synthase catalyzing the biosynthesis of tryptophan (primary precursor of indoles), but also stimulate IAA synthesis. Thus, the contribution of Zn to the formation of PAS is high. The effects of Cu and Zn on PAS metabolism may be mediated via oxidation–reduction reactions, which enhance the energy potential of cells.

4. THERAPY AND PREVENTION OF MICROELEMENTOSES

The ability of medicinal plants to concentrate various elements is of considerable theoretical, as well as practical, interest. This should be taken into account in studying the regulation of PAS metabolism. This property opens new possibilities for using medicinal plants in medical practice. Medicinal plant cultivation can be intensified by elaborating new agricultural technologies.

Metabolic diseases associated with disturbances in the microelement balance received the name microelementoses. These disorders accompany genetic diseases or result from an excess or low supply of microelements [3, 15, 55, 56]. Such disturbances include cardiovascular diseases (Cr, Se, and Mn deficiency), nervous diseases (Mn deficiency), dwarfism, retarded sexual development, alopecia, parakeratosis (Zn deficiency), thyroid gland disease (J deficiency), and psychotic disorders (Li deficiency). In addition to microelementoses, borderline disorders related to the adverse effects of environmental factors should be prevented.

Soluble mineral salts are widely used medicines containing microelements. However, these compounds are characterized by low assimilability after peroral administration (not more than 3–10%). Therapeutic doses of soluble mineral salts are ten times higher than their biotic concentrations, which can lead to overdosing and delayed side effects associated with individual differences in the assimilability of individual elements or groups of elements. The use of medicinal plants as the source of microelements allows us to prevent these adverse consequences.

It was previously hypothesized that the pharmacological activity of medicinal plants depends on the presence of PAS. This hypothesis underwent revisions when the ability of medicinal plants to concentrate biologically important elements was demonstrated. The therapeutic effect of medicinal plants is believed to be primarily associated with this property. As the source of microelements, medicinal plants have some advantages over mineral salts. Plants contain microelements in the organically bound (easily assimilable) form, which allows us to decrease their therapeutic doses. Therefore, the risk for overdosing also decreases. Daily doses of medicinal plants (concentrators and, especially, overconcentrators of elements) include Co, Zn, Mn, Cr, and Se at concentrations necessary for the therapy of microelementoses. To prevent disturbances in the microelement balance, medicinal plants should be used in patients with chronic diseases or at the initial stage of disorders. During the acute stage of a disease, mineral salts are more potent than plants [3, 57].

The advantage of medicinal plants is that their mineral complex contains all essential components in the optimal ratio. It is difficult to synthesize drugs of such adequate composition, because the role of synergistic and antagonistic interrelations between various elements in living organisms is poorly understood. Moreover, microelements present in medicinal plants can enhance the therapeutic effect of their major components. The introduction of adonis ash (*Adonis vernalis* L.) into the complex preparation of Fikomin potentiates its therapeutic effect on the myocardium [3]. It should be emphasized that medicinal plant ashes were used in traditional (e.g., Tibetan) medicine [10].

PAS and elements accumulated at high doses by medicinal plants potentiate the effects of each other, which enhances their pharmacological activities. Codirected effects of PAS and elements are observed in medicinal plants used for the treatment of cardiovascular diseases and atherosclerosis. These medicinal plants, including digitalis, common foxglove, *Dioscorea deltoidea*, *Dioscorea nipponica*, cudweed, *Phlojodicarpus sibiricus* (Steph. Ex Spreng.) K. Pol, periwinkle (*Vinca minor* L.), puncture weed (*Tribulus terrestris* L.), skullcap (*Scutellaria baicalensis* Georgi), and hawthorn, concentrate Cr (even at overdoses) with marked antisclerotic properties [17]. Medicines used for the treatment of chronic cardiac insufficiency and cardiosclerosis are prepared from common foxglove (78 C).

Cudweed (56 C) and *Phlojodicarpus sibiricus* (Steph. Ex Spreng.) K. Pol (38 C) are overconcentrators of Cr. *Phlojodicarpus sibiricus* (Steph. Ex Spreng.) K. Pol plants enter the composition of antisclerotic Flowjerin used for the treatment of Raynaud's phenomenon, spastic endarteritis, and obliterating endarteritis (a severe disease of the vessels of the upper and lower limbs). *Dioscorea nipponica* plants (12 C, Cr overconcentrator) serve as the raw material for polysponin (antisclerotic phytopreparation). Polysponin decreases blood cholesterol concentration and inhibits the buildup of cholesterol deposits in the vessel walls (this preparation retains cholesterol in the colloidal state) [58].

Studies of medicinal plants that accumulate Se, Mn, and Li demonstrated the similarity of effects produced by PAS and concentrated elements. Anticarcinogenic activities of vinblastine, one of the most potent cytostatic derived from *Catharanthus roseus* (CBA 10) and alkaloids of celandine (*Chelidonium majus* L., CBA 12) are potentiated by Se. The tonic effect of small-leaved China plant (*Thea sinensis* L.) depends not only on the presence of tannin and caffeine (major PAS in these plants), but also on the amount of Mn (18 C). Mn ions activate carboxylase, aminopeptidase, galactotransferase, arginase, alkaline phosphatase, and other enzymes, catalyze reactions of carbohydrate, protein, and phosphorus metabolism, and are involved in basal metabolism [59].

Eighteen plant species are Li concentrators. Overconcentrators of Li, henbane (*Hyoscyamus niger* L.), datura (*Datura innoxia* Mill.), and belladonna (*Atropa belladonna* L.), synthesize tropane alkaloids, including scopolamine. Scopolamine hydrobromide is widely used in psychiatry and neurology for the therapy of Parkinson's disease. Li ions produce similar effects. Li deficiency underlies the development of nervous and

psychotic disorders. It was reported that Li ions produce good effects in patients with schizophrenia [5].

Such examples are numerous. However, PAS and elements do not necessarily produce fully identical effects. Many plant species contain PAS whose pharmacological activity differs from that of accumulated elements. These elements provide medicinal plants with new therapeutic properties, which are sometimes underestimated or disregarded. For example, *Glycyrrhiza glabra* and *C. uralensis* are used for the treatment of gastritis, stomach and duodenal ulcers, bronchial asthma, and allergic dermatitis. These therapeutic effects are related to the presence of glycyrrhizin (triterpene saponin). At the same time, *Glycyrrhiza uralensis* plants are overconcentrators of Se (11 C), producing a modulatory effect on the cardiovascular system. These medicinal plants can be used for the treatment and prevention of cardiomyopathies, which is important when considering the conditions of Se deficiency in many Russian regions. Thus, medicinal plants hold much promise as the source of various elements.

5. INTENSIFICATION OF MEDICINAL PLANT CULTIVATION

The ability of medicinal plants to concentrate elements, as well as their role as regulators of PAS metabolism, allowed the development of theoretical principles of medicinal plant cultivation. These studies resulted in the creation of new technologies of medicinal plant cultivation that increased the yield of high-quality raw materials. An improvement in plant materials is achieved by increasing the content of PAS (active ingredients) and biologically important elements. This is very important because *In vivo* enrichment of medicinal plants with these elements promotes the synthesis and accumulation of PAS and contributes to the appearance of new therapeutic properties. For example, treatment of common foxglove with J stimulates biological activity and decreases plant toxicity [60–63].

New cultivation technologies include treatment of plants with elements playing the role of cofactors or activators of the enzymes involved in PAS metabolism. These elements are Co and Zn for indoles, Co for tropanes and phenolic compounds, and Mn for terpenoids. Some plant species are treated not only with elements, but also with growth regulators and phytohormones. The regimen of treatment depends on the plant species and cultivation conditions. Metals, phytohormones, and growth regulators producing similar effects potentiate the influences of each other. Cr and Se are recommended to be used as microfertilizers during cultivation of plant species whose ability to accumulate these elements is not completely realized (which is confirmed by high CBA values and low absolute content of Cr and Se). This is typical of plants (moderate concentrators) grown on soil with a low content of Cr and Se. Agricultural treatment will result in the appearance of new overconcentrators of Cr and Se. The use of Cr as a microfertilizer during cultivation of *Dioscorea deltoidea* and *Rosa majalis*, as well as the addition of Se during the growth of *Macleaya cordata* (Wild) R. Br., *Hedysarum alpinium* L., wild marjoram (*Origanum vulgare* L.), and black currant having high CBA values (above 40 for Se, standard 1), is substantiated.

A peculiar feature of medicinal plants is their ability to synthesize and accumulate considerable amounts of nearly all kinds of PAS that may coexist in many species. Moreover, medicinal plants concentrate individual elements or groups of five to ten elements. These interrelated processes are realized via various stages of molecular regulation. The synthesis of PAS and accumulation of elements typical of medicinal plants contribute to species specificity and, therefore, determine their pharmacological properties. The chemical peculiarities of medicinal plants contribute to their wide use in the treatment and prevention of microelementoses, as well as to the intensification of medicinal plant cultivation.

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