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PHENYLPROPANOIDS FROM MEDICINAL PLANTS: DISTRIBUTION, CLASSIFICATION, STRUCTURAL ANALYSIS, AND BIOLOGICAL ACTIVITY

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*The literature and our own research results on phenylpropanoids from medicinal plants were reviewed and systematized. Data were presented for the distribution of phenylpropanoids. Their classification was proposed. The biological structure—activity relationships for compounds found in roseroot (*Rhodiola rosea*), thorny eleutherococcus (*Eleutherococcus senticosus*), common lilac (*Syringa vulgaris*), purple echinacea (*Echinacea purpurea*), medicinal melissa (*Melissa officinalis*), variegated milk-thistle (*Silybum marianum*), and others were discussed.*

Key words: phenylpropanoids, cinnamic alcohols, cinnamic acids, lignans, flavolignans, medicinal plants, immunomodulator, hepatoprotector, antioxidant, roseroot (*Rhodiola rosea*), thorny eleutherococcus (*Eleutherococcus senticosus*), common lilac (*Syringa vulgaris*), purple echinacea (*Echinacea purpurea*), medicinal melissa (*Melissa officinalis*), variegated milk-thistle (*Silybum marianum*).

Phenylpropanoids, which contain one or several C_6-C_3 fragments, are widely distributed in nature but have only recently attracted the attention of researchers searching for promising biologically active compounds (BAC) and synthesizing effective medicines based on them.

Cholagogues based on caffeoylquinic acids of artichoke and Italian everlasting [1, 2] and hepatoprotector medicinal preparations based on flavolignans of variegated milk-thistle [*Silybum marianum* (L.) Gaertn.] [3-7] have relatively recently been incorporated into medical practice. Antimicrobial, antiviral, and immunostimulating properties of hydroxycinnamic acids and their derivatives [8-13] and stimulating properties of cinnamyl alcohol glycosides found in roseroot rhizomes (*Rhodiola rosea* L.) [14-16] and thorny eleutherococcus [*Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim.] [17-19] have been discovered.

A targeted search for phenylpropanoids with stimulating and adaptogenic properties revealed cinnamyl alcohol glycosides, which we called cinnamylglycosides [20], in promising medicinal plants such as basket willow and common lilac (*Syriniga vulgaris* L.) [16, 21-24] and in tissue- and cell-culture biomass of roseroot [25, 26]. The chemical and spectral properties and the biological activity depend on the phenylpropanoid structure [16, 21, 27]. The resulting trends provided a basis for methodic approaches to the standardization of medicinal plant material and phytopreparations containing cinnamylglycosides and were also used to develop a new concept for creating preparations based on roseroot rhizomes [25, 27-37].

Our goal was to categorize and systematize this literature and the results of our own research on phenylpropanoids showing promise as BAC.

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1. CLASSIFICATION AND NOMENCLATURE OF PHENYLPROPANOIDS

A large number of new phenylpropanoids has been found. However, there is still no generally accepted classification of this group of compounds. The nomenclature used by various investigators in discussing the structures of phenylpropanoids is unwieldy.

Phenylpropanoids can conveniently be treated as a large class of natural compounds consisting of the following groups:

1. Simple phenylpropanoids:
    a) cinnamyl alcohols and their derivatives (ethers, glycosides);
    b) cinnamic acids and their derivatives (esters, glycosides, other derivatives);
    c) cinnamamides;
    d) cinnamaldehydes;
    e) phenylpropanes.
2. Complex phenylpropanoids:
    a) phenylpropanoid glycosides based on phenylethanes;
    b) oxidative coupling products (lignoids): flavolignans; xanthonolignans; coumarinolignans; alkaloidolignans; neolignans; lignans (dimers and oligomers of phenylpropanoids).
3. Biogenetically related phenylpropanoids (flavonoids, coumarins, etc.).

The classification of phenylpropanoids proposed by us is based on current impressions of the biosynthesis of phenolic compounds, in which cinnamyl alcohols **1-4** and cinnamic acids **5-10** play key roles. The literature on the distribution in plants of the most important phenylpropanoids (groups 1 and 2) is presented according to this classification. Flavonoids and coumarins, the biogenetic precursors of which are phenylpropanoids, can be usefully reviewed according to an overall classification only from the viewpoint of biosynthesis. These compounds have been described in detail as independent classes of natural compounds in monographs and reviews [38].

Compounds **1**, **5**, **8**, **33**, and **42** provide an example of the usefulness of using a conventional numbering for the phenylpropanoid carbon atoms that enables the propane fragment in the molecule (C-7, C-8, and C-9) to be clearly identified. For example, these correspond to the frequently used notation (C-*a*, C-β, and C-γ). This reveals structural features of the various groups in phenylpropanoids. In our opinion, this approach is especially critical for interpreting and comparing spectral data during structural analyses using ^{1}H and ^{13}C NMR spectroscopy and other methods.

2. DISTRIBUTION OF PHENYLPROPANOIDS IN PLANTS

The literature on the distribution in plants of the most important phenylpropanoids indicates that plants of the families composites or asters (Asteraceae), orpines (Crassulaceae), aralias (Araliaceae), figworts (Scrophulariaceae), willows (Salicaceae), plantains (Plantaginaceae), mezereums (Thymelaeaceae), mints (Lamiaceae), and olives (Oleaceae) are rich sources of BAC.

This section examines in detail phenylpropanoids of original structure that are of greatest interest for structural studies or biological activity. These are primarily phenylpropanoid glycosides **11-17**, **20-24**, **28-32**, and **43-46**; flavolignans **33-36**; xanthonolignan **37**; coumarinolignan **38**; neolignans **39** and **40**; and lignans **41-48**, which have been studied systematically only recently. Thus, roseroot, thorny eleutherococcus, purple echinacea, medicinal melissa, variegated milk-thistle, and common lilac have been described in most detail. These are of greatest interest as promising sources of medicinal preparations [3, 6, 7, 10, 12, 18, 20, 24, 35, 37].

Extensive data on the distribution of well-known compounds such as *p*-coumaric, caffeic, ferulic, and sinapic acids **5-10**, cinnamyl alcohols **1-4**, and certain other compounds are not presented because they have been discussed in monographs [37-41]. The most interesting simple phenylpropanoids with respect to biological activity and structural analysis are cinnamyl alcohol glycosides **11-17** and derivatives of cinnamic acids **18-24**. Compounds lacking an oxygenated functional group in the propane fragment (phenylpropanes) occupy a special place among simple phenylpropanoids. Only the most familiar examples are given: anethole (**27**), estragole (**25**), and eugenol (**26**). Nevertheless, this family of compounds is widely distributed in plants [12, 40-42]. They not only are a component of essential oils but also can occur as glycosylated forms, e.g., eugenol [43]. It is

important to consider that glycosides are cleaved to the corresponding aglycons during enzymatic processes (for example, during slow drying), which can increase the content of essential oil in the plant material. Experience teaches that this is not always taken into account in comparing data on the content of essential oil in various samples of a single species of medicinal plant.

Structures of phenylpropanoid glycosides vary owing to changes in the C_6-C_3 fragment, the carbohydrate, and other structural units in the molecules. The most numerous group of glycosides includes derivatives of phenylethanes (complex phenylpropanoids **28**-**32**), the distribution of which in plants has been reviewed in a foreign journal [11] and monograph [37]. Reports of the isolation of new glycosides of interest for chemical systematics, structural analysis, and biological activity have appeared [37, 44-51].

Lignoids based on flavonoids (flavolignans **33**-**36**), xanthones (xanthonolignan **37**), and coumarins (coumarinolignan **38**) belong to a comparatively small group. Structural analyses of these and data on their distribution in plants have been reviewed in detail [3]. Furthermore, the first communication about the isolation of a lignoid based on an alkaloid appeared recently [52]. This provided a basis for us to assign acrignine A to a new group of compounds, alkaloidolignans [37]. The biosynthesis of these compounds is interesting because the formation of lignoids, like that of lignans, is based on oxidative coupling [3, 38, 53, 54]. Investigations of the biosynthesis mechanism of lignans of *Forsythia intermedia* (Oleaceae) deserve special attention [53, 54]. In particular, it was shown that phenylalanine and ferulic acid (**8**) are good biogenetic precursors of arctigenin, epipinoresinol, and phyllogenin, which are formed via oxidative coupling of two molecules of coniferyl alcohol (**3**) according to the scheme: ferulic acid → feruloyl-S-CoA → coniferyl aldehyde → coniferyl alcohol → lignan. It is interesting that a suspension culture of *F. intermedia* accumulates up to 10% lignan glycosides (of air-dried mass) [53, 54].

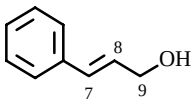
Lignans and their glycosides **41**-**48** include examples that illustrate only the variety of this class and compounds for which the biological activity has been discussed. However, this group of compounds is widely distributed in plants and is represented by not only benzylphenyltetrahydrofurans **41**-**44**, diphenylfurofurans **45** and **46**, and dibenzocyclooctanes **47** and **48**, but also other derivatives [40, 41, 55].

Glucosides of *p*-coumaric and ferulic acids, which accumulate in suspension culture of *Chemopodium rubrum*, exhibit high metabolic activity [47, 55]. It has been hypothesized that the aforementioned metabolites may participate in the formation of more complex phenylpropanoids. Information on the formation of cinnamic acids, cinnamyl alcohols, and lignans and their glycosides in many other tissue- and cell-cultures of medicinal plants has been published [37]. This indicates that the acetate—malonate pathway occurs more often than not during in vitro biosynthesis of plant substances [38].

The data presented below will be useful for discussing methods of isolating phenylpropanoids and analyzing their structures and for resolving issues connected with the standardization of medicinal plant material and the creation of preparations based on substances containing phenylpropanoids.

CINNAMYL ALCOHOLS

1. Cinnamyl alcohol



Rhodiola rosea L. (rhizome), Crassulaceae [20]; *Rhodiola arctica* Boriss. (rhizome) [56]

$C_9H_{10}O$ (M^+ 134)

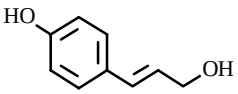
mp: 33-34°C ($CHCl_3$—hexane)

UV: 252 nm

Mass (20°): 134 (70) $[M]^+$, 115 (40), 105 (52), 92 (100), 91 (80), 78 (80), 77 (50)

PMR (CD_3COCD_3): 7.2-7.4 (5H, m, Ar-H), 6.65 (1H, d, J = 16.0, H-7), 6.4 (1H, dt, J = 6.0, J = 16.0, H-8), 4.3 (2H, m, H-9) [20]

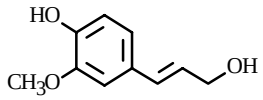
Biological activity: weak tonic [16]



2. *p*-Coumaryl alcohol

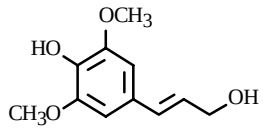
Rhodiola rosea L. (callus culture) [25, 57]
$C_9H_{10}O_2$ (M^+ 150)

mp: 116-118°C (H_2O)
UV: 264 nm
Mass (100°): 150 (100) $[M]^+$, 149 (7), 134 (1), 133 (11), 132 (25), 122 (2), 108 (22), 107 (100), 103 (38), 94 (95)
PMR (CD_3COCD_3, 100 MHz, ppm, J/Hz): 7.2-7.4 (5H, m, Ar-H), 6.65 (1H, d, J = 16.0, H-7), 6.4 (1H, dt, J = 6.0, J = 16.0, H-8), 4.3 (2H, m, H-9) [25]
Biological activity: weak tonic [16]



3. Coniferyl alcohol

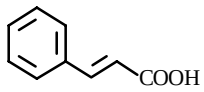
Vanillia mexicana Mill., Orchidaceae [40]
$C_{10}H_{12}O_3$ (M^+ 180)
mp: 74-75°C
Mass (100°): 180 (39) $[M]^+$, 167 (48), 163 (46), 152 (4), 151 (3), 149 (100), 137 (6), 136 (11), 124 (4), 117 (7), 115 (3), 91 (50) [36]



4. Synapyl alcohol

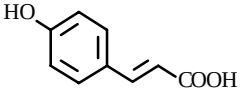
Eleutherococcus senticosus (Rupr. et Maxim.) Maxim. (roots), Araliaceae [19]
$C_{10}H_{12}O_3$ (M^+ 210)
mp: 63-65°C
Mass (70°): 210 (4) $[M]^+$, 183 (7), 182 (100), 181 (48), 168 (10), 167 (48), 155 (3), 154 (2), 153 (4), 152 (1), 151 (3), 150 (6), 149 (60) [19]

CINNAMIC ACIDS



5. Cinnamic acid

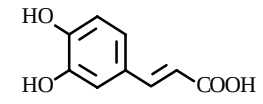
Populus laurifolia Ledeb. (buds), Salicaceae [37]
$C_9H_8O_2$ (M^+ 148)
mp: 119-121°C ($CHCl_3$—hexane) [37]



6. *p*-Coumaric acid

Cerasus serrulata Don. (flowers), Rosaceae [58]; *Rhodiola rosea* L. (biomass), Crassulaceae [25]; *Populus balsamifera* L. (buds), Salicaceae [37]; *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (roots), Araliaceae [59]

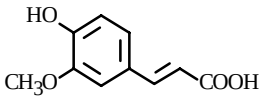
$C_9H_8O_3$ (M^+ 164)
mp: 207-209°C ($CHCl_3$—CH_3OH)
UV: 227, 295 sh, 309 nm [25]
Biological activity: antimicrobial activity [159]



7. Caffeic acid

Cerasus serrulata Don. (flowers), Rosaceae [58]; *Rhodiola rosea* L. (rhizome), Crassulaceae [19]; *Melissa officinalis* L. (herb), Lamiaceae [12, 60]; *Populus balsamifera* L. (buds), Salicaceae [37]

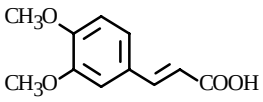
$C_9H_8O_4$ (M^+ 180)
mp: 218-222°C (aqueous acetone)
UV: 247, 299, 327 nm
Mass (100°): 180 (100) $[M]^+$, 163 (31), 152, 136
PMR (CD_3COCD_3, 100 MHz, ppm, J/Hz): 7.56 (1H, d, J = 16.0, H-7), 7.2 (1H, s, H-2), 7.14 (1H, d, J = 9.0, H-6), 6.88 (1H, d, J = 9.0, H-5), 6.28 (1H, d, J = 16.0, H-8) [25]
Biological activity: antimicrobial activity [159]



8. Ferulic acid

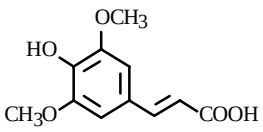
Eleutherococcus senticosus (Rupr. et Maxim.) Maxim. (roots), Araliaceae [59]; *Populus balsamifera* L. (buds), Salicaceae [37]

$C_{10}H_{10}O_4$ (M^+ 194)
mp: 168-170°C (aqueous alcohol)
UV: 242, 292, 324 nm
PMR (CD_3COCD_3, 100 MHz, ppm, J/Hz): 8.14 (1H, d, J = 16.0, H-7), 7.68 (1H, d, J = 2.0, H-6), 7.24 (1H, dd, J = 2.0, J = 9.0, H-2), 6.98 (1H, d, J = 9.0, H-5), 6.90 (1H, d, J = 16.0, H-8), 3.80 (3H, s, CH_3O) [37]
Biological activity: antimicrobial activity [159]



9. 3,4-Dimethoxycinnamic acid

Populus balsamifera L. (buds), Salicaceae [37]
$C_{11}H_{12}O_4$ (M^+ 206)
mp: 142-145°C (aqueous acetone)
PMR (CD_3COCD_3, 100 MHz, ppm, J/Hz): 7.44 (1H, d, J = 16.0, H-7), 7.26 (1H, d, J = 2.0, H-6), 7.14 (1H, dd, J = 2.0, J = 9.0, H-2), 7.00 (1H, d, J = 9.0, H-5), 6.43 (1H, d, J = 16.0, H-8), 3.98 (3H, s, CH_3O), 3.96 (3H, s, CH_3O) [37]

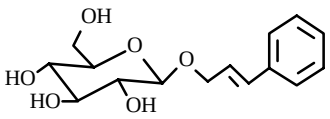


10. Sinapic acid

Brassica oleracea (leaves), Brassicaceae [40]
$C_{11}H_{12}O_5$
mp: 191-192°C (aqueous alcohol) [40]

THE MOST IMPORTANT PHENYLPROPANOIDS AND THEIR DISTRIBUTION IN PLANTS

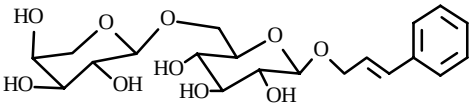
CINNAMYL ALCOHOLS AND THEIR DERIVATIVES



11. Rosin

Rhodiola rosea L. (rhizome), Crassulaceae [20];
Rhodiola arctica Boriss. (rhizome) [56]

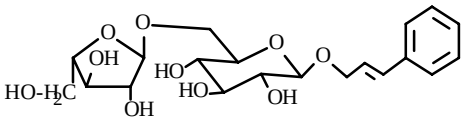
$C_{15}H_{20}O_6$, colorless glassy substance
$[\alpha]_D^{20}$ -44.8° ($CHCl_3$—CH_3OH)
UV: 252 nm
Mass (160°): 296 (0.3) $[M]^+$, 134 (13), 133 (13), 127 (6), 118 (75), 117 (100), 115 (45), 91 (56)
PMR (CD_3COCD_3, 100 MHz, ppm, J/Hz): 7.2-7.4 (5H, m, Ar-H), 6.70 (1H, d, J = 16.0, H-7), 6.40 (1H, dt, J = 6.0, J = 16.0, H-8), 4.2-4.7 (2H, dq, J = 6.0, J = 13.0, H-9), 4.46 (1H, d, J = 7.0, H-1′), 3.3-4.0 (6H, m, glucose protons) [20]
Biological activity: tonic [16]



12. Rosavin

Rhodiola rosea L. (rhizome), Crassulaceae [20];
R. arctica Boriss. (rhizome) [56]
$C_{20}H_{28}O_{10}$

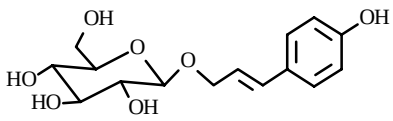
mp: 171-173°C (ethanol)
$[\alpha]_D^{20}$ -56.5° ($CHCl_3$—CH_3OH)
UV: 252 nm
Mass (140°): 286 (5), 220 (4), 219 (5), 162 (6), 145 (9), 143 (9), 134 (31), 133 (34), 118 (46), 118 (75), 117 (100), 115 (60)
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 7.2-7.4 (5H, m, Ar-H), 6.82 (1H, d, J = 16.0, H-7), 6.50 (1H, dt, J = 6.0, J = 16.0, H-8), 4.94 (1H, d, J = 7.0, H-1′), 4.87 (1H, d, J = 6.0, H-1″), 4.66-4.98 (2H, m, H-9), 3.95-4.55 (10H, m, sugar protons), 3.70 (2H, q, J = 2.0, J = 13.0, H-5e″) [20]
Biological activity: tonic [16]



13. Rosarin

Rhodiola rosea L. (rhizome), Crassulaceae [20];
R. arctica (rhizome) [56]
$C_{20}H_{28}O_{10}$, colorless glassy substance

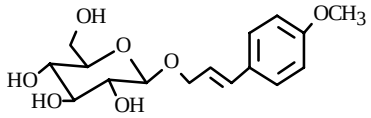
UV: 252 nm
$[\alpha]_D^{20}$ -76.1° ($CHCl_3$—CH_3OH)
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 7.2-7.4 (5H, m, Ar-H), 6.78 (1H, d, J = 16.0, H-7), 6.50 (1H, dt, J = 6.0, J = 16.0, H-8), 5.75 (1H, d, J = 2.0, H-1″), 4.82 (1H, d, J = 7.0, H-1′), 4.36-4.95 (2H, m, H-9), 3.9-4.3 (11H, m, sugar protons) [20]
Biological activity: tonic [16]



14. Triandrin

Rhodiola rosea L. (callus tissue) Crassulaceae [25];
Salix triandra L. (bark), Salicaceae [61]; *Lilium cordatum* (Thunb.) Loidz. (petals), Liliaceae [62]
$C_{15}H_{20}O_7 \cdot H_2O$

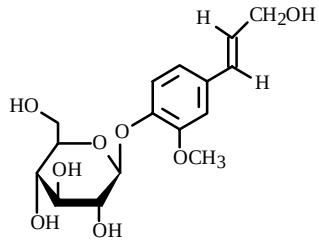
mp: 178-180°C (H_2O)
$[\alpha]_D^{20}$ -62.3° (H_2O)
UV: 264 nm
Mass (250°): 150 (12), 149 (23), 148 (10), 147 (8), 134 (31), 133 (85), 132 (96), 121 (15), 108 (2), 107 (15), 103 (100)
PMR (CD_3COCD_3, 250 MHz, ppm, J/Hz): 7.4 (2H, d, J = 8.5, H-2, H-6), 7.14 (2H, d, J = 8.5, H-3, H-5), 6.73 (1H, d, J = 16.0, H-7), 6.35 (1H, d, J = 6.0, J = 16.0, H-8), 5.00 (1H, d, J = 7.8, H-1′), 4.76 (1H, ddd, J = 12.5, J = 6.0, J = 1.5, H-9), 4.60 (1H, dd, J = 2.5, J = 12.0, H-6′), 4.44 (1H, dd, J = 6.0, J = 12.5, H-9), 3.9-4.35 (4H, m, glucose protons) [25]
Biological activity: tonic [16]



15. Vimalin

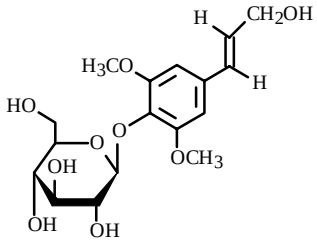
Rhodiola rosea L. (callus tissue), Crassulaceae [25]; *Salix viminalis* L. (bark), Salicaceae [63]
$C_{16}H_{22}O_7 \cdot H_2O$

mp: 143-144°C (H_2O)
$[\alpha]_D^{20}$ -60.6 (H_2O)
UV: 262 nm
Mass (150°): 164 (44), 163 (19), 148 (94), 147 (100), 134 (6), 133 (6), 132 (12), 122 (12), 121 (38), 108 (13) [25]



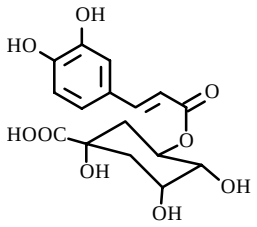
16. Coniferin

Syringa vulgaris L. (bark), Oleaceae [64]; *Lilium cordanum* (Thunb.) Koidz. (petals), Liliaceae [62]; *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (roots), Araliaceae [59, 64]
$C_{16}H_{22}O_8$
mp: 143-144°C (H_2O)
$[\alpha]_D^{20}$ -60.6° (H_2O)
UV: 258, 266 (sh) nm
Mass (190°): 180 (100), 152 (3), 151 (2.5), 138 (4), 137 (26), 124 (20), 115 (1), 103 (4), 91 (4) [64]



17. Syringin (Eleutheroside B)

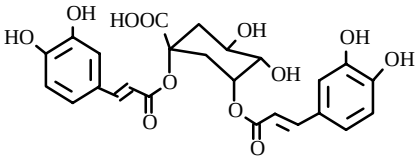
Syringa vulgaris L. (bark) [64], *S. amurensis* (bark) [65], (leaves), Oleaceae [36]; *Lilium cordatum* (Thunb.) Koidz. (petals), Liliaceae [62]; *Codonopsis tangshen* Oliv. (roots), Campanulaceae [66]; *Eleutherococcus senticosus* (bark, roots) [55, 59, 67-69]
$C_{17}H_{24}O_9$
mp: 190-192°C (H_2O)
$[\alpha]_D^{19}$ -29.0° (ethanol)
UV: 266 nm
Mass (160°): 210 (100), 209 (3), 194 (15), 181 (11), 177 (26), 167 (35), 154 (20), 149 (28), 124 (10), 105 (10), 103 (4), 91 (17)
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 6.88 (1H, d, J = 16.0, H-7), 6.86 (2H, s, H-2, H-6), 6.65 (1H, d, J = 7.0, H-1′), 6.60 (1H, dt, J = 6.0, J = 16.0, H-8), 4.1-4.7 (8H, m, 2H-9 + 6H glucose), 3.76 (6H, s, 2×CH_3O) [64]
Biological activity: tonic [16]



18. Chlorogenic acid

Eleutherococcus senticosus (Rupr. et Maxim.) Maxim. (roots), Araliaceae [19, 59]; *Helichrysum italicum* Guss. (flowers), Asteraceae [1]
$C_{16}H_{18}O_9$
mp: 203-205°C (H_2O)
UV: 243, 300 sh, 330 nm

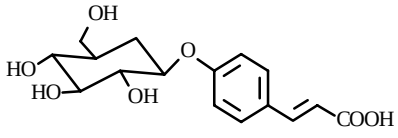
PMR (DMSO-d_6, 100 MHz, ppm, J/Hz): 7.45 (1H, d, J = 16.0, H-7), 7.06 (1H, d, J = 2.0, H-2′), 7.0 (1H, dd, J = 2.0, J = 8.0, H-6′), 6.80 (1H, d, J = 8.0, H-5′), 6.18 (1H, d, J = 16.0, H-8), 5.10 (1H, dt, J = 5.0, J = 9.0, H-5), 4.00 (1H, q, J = 3.0, H-3), 3.62 (1H, dd, J = 3.0, J = 9.0, H-4) [1]
Biological activity: cholagogue [37]



19. 1,3-Dicaffeoylquinic acid (cynarin)

Helichrysum italicum Guss. (flowers), Asteraceae [1]
$C_{25}H_{24}O_{12}\cdot H_2O$
mp: 226-228°C (H_2O) (dec.)
UV: 245 sh, 300 sh, 330 nm

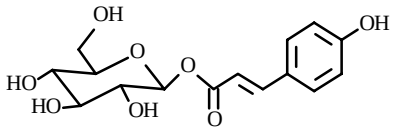
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 8.0 and 7.92 (2d, J = 16 Hz, 2H-7), 7.5-6.8 (m, 6H-Ar + H-8), 6.55 (d, J = 16, H-8), 6.22 (H-3), 5.08 (H-5), 4.36 (H-4), 3.6-2.6 (m, 2H-2 and 2H-6) [1]
Biological activity: cholagogue [37]



20. *p*-Coumaric acid 4-O-*β*-D-glucopyranoside

Rhodiola rosea L. (tissue culture) [25]
$C_{15}H_{18}O_8$
mp: 238-240°C ($CHCl_3$—CH_3OH)
UV: 261 nm

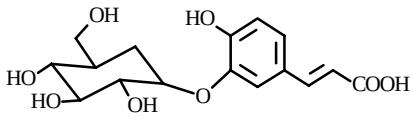
PMR (C_5D_5N, 250 MHz, ppm, J/Hz): 7.96 (1H, d, J = 16.0, H-7), 7.52 (2H, d, J = 9.0, H-2, H-6), 7.18 (2H, d, J = 9.0, H-3, H-5), 6.74 (1H, d, J = 16.0, H-8), 5.64 (1H, d, J = 7.5, H-1′), 4.53 (1H, dd, J = 12.0, J = 2.5, H-6′), 4.1-4.4 (5H, m, glucose protons) [25]



21. *p*-Coumaric acid 1-O-*β*-D-glucopyranoside (melilotoside)

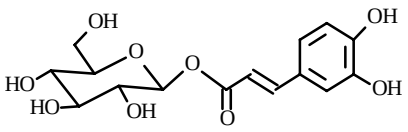
Rhodiola rosea L. (tissue culture) [25]
$C_{15}H_{18}O_8$
mp: 223-224°C (ethanol)
UV: 230, 317 nm

PMR (C_5D_5N, 250 MHz, ppm, J/Hz): 7.94 (1H, d, J = 16.0, H-7), 7.48 (2H, d, J = 9.0, H-2, H-6), 7.10 (2H, d, J = 9.0, H-3, H-5), 6.54 (1H, d, J = 16.0, H-8), 6.48 (1H, d, J = 7.5, H-1′), 4.48 (1H, dd, J = 12.0, J = 2.5, H-6′), 4.1-4.4 (5H, m, glucose protons) [25]



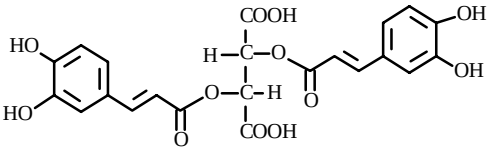
22. Caffeic acid 3-O-β-D-glucopyranoside

Rhodiola rosea L. (tissue culture) [25]
$C_{15}H_{18}O_9$
mp: 195-198°C ($CHCl_3$—CH_3OH)
UV: 227, 295, 311 nm
PMR (C_5D_5N, 250 MHz, ppm, J/Hz): 7.96 (1H, d, J = 16.0, H-7), 7.90 (1H, d, J = 1.7, H-2), 7.27 (1H, dd, J = 8.5, J = 1.7, H-6), 7.14 (1H, d, J = 8.5, H-5), 6.77 (1H, d, J = 16.0, H-8), 5.53 (1H, d, J = 7.5, H-1′), 4.66 (1H, dd, J = 12.0, J = 2.0, H-6′), 3.9-4.4 (5H, m, glucose protons) [25]



23. Caffeic acid 1-O-β-D-glucopyranoside

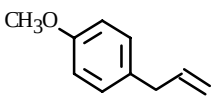
Cerasus serrullata Don. (flowers), Rosaceae [58]
$C_{15}H_{18}O_9$
mp: 182-184.5°C (ethanol)
UV: 217, 235, 299, 327 nm
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 7.97 (1H, d, J = 16.0, H-7), 7.54 (1H, d, J = 2.0, H-2), 7.22 (1H, d, J = 9.0, H-5), 7.08 (1H, dd, J = 9.0, J = 2.0, H-6), 6.56 (1H, d, J = 16.0, H-8), 6.50 (1H, d, J = 7.0, H-1′), 4.0-4.5 (6H, m, glucose protons) [58]



24. 2,3-Dicaffeoylquinic acid (cichoric acid)

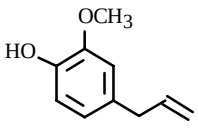
Echinacea angustifolia (leaves), Asteraceae [70]; *E. pallida* Nutt. (leaves) [10]; *E. purpurea* L. (leaves) [9]; *Cichorium endivia* L. (Asteraceae) [72, 73]; *C. intybus* L. (leaves) [37]
$C_{22}H_{18}O_{12}$, amorphous substance [70]
mp: 204-206°C [72, 73]
$[\alpha]_D^{25}$ +374° (CH_3OH)
Biological activity: immunostimulant [39]

PHENYLPROPANES



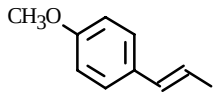
25. Estragole (methylchavicole, isoanethole)

Artemisia dracunculus L. (herb), Asteraceae [37, 40]
$C_{10}H_{12}O$, oily liquid
bp: 215-216°C [40]



26. Eugenol

Caryophyllus aromaticus L. = *Eugenia caryophyllata* Thunb. (buttons), Caryophyllaceae [37, 40]
$C_{10}H_{12}O_2$, oily liquid
bp: 248-252°C
Biological activity: antimicrobial activity [37]

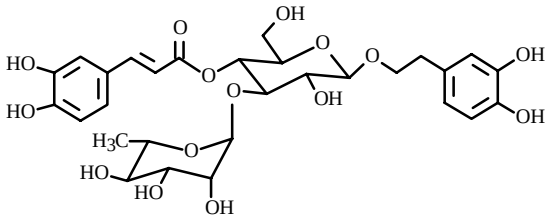


27. Anethole

Foeniculum vulgare Mill. (fruit), Apiaceae [37, 40]
$C_{10}H_{12}O$

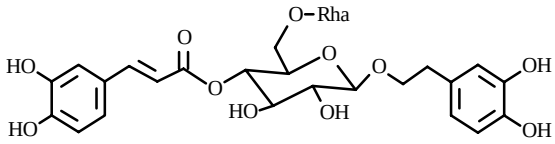
mp: 21.5-22.5°C (ethanol) [40]
Biological activity: expectorant [37]

PHENYLPROPANOID GLYCOSIDES BASED ON PHENYLETHANOIDS



28. Acteoside (verbascoside)

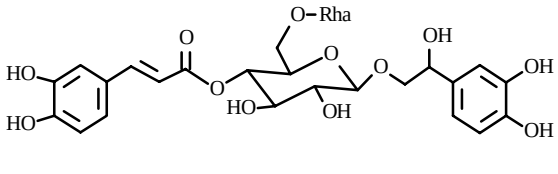
Syringa vulgaris L. (bark) [64], (flowers), Oleaceae [74]; *Digitalis purpurea* L. (callus culture of leaves), Scrophulariaceae [75]; *Verbascum sinuatum* L. (herb), Scrophulariaceae [41]; *Castilleja liniariaefolia* Benth. (leaves, roots), Scrophulariaceae [76]; *Rhemania glutinosa* (callus culture), Scrophulariaceae [77]; *Plantago crassifolia* (leaves and roots), Plantaginaceae [11]; *Stachys seedlings* (leaves), Lamiaceae [11]
$C_{29}H_{36}O_{15}\cdot H_2O$
mp: 147-150°C (H_2O)
$[\alpha]_D$ -85.6° (CH_3OH)
UV: 242, 299 sh, 330 nm
Mass (260°): 316 (13), 180, 163, 154 (53), 137 (46), 136 (39), 123 (100)
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 7.45 (1H, d, J = 16.0, H-7‴″), 6.6-7.30 (5H, m, H-Ar), 6.75 (1H, d, J = 16.0, H-8‴″), 6.28 (1H, d, J = 2.0, H-2), 5.70 (1H, t, J = 9.5, H-4″), 4.80 (1H, d, J = 7.0, H-1″), 4.78 (1H, br.s, H-1‴), 3.9-4.6 (9H, m, sugar protons), 3.85 (2H, t, J = 7.0, H-8), 2.92 (2H, t, J = 7.0, H-7), 1.64 (3H, d, J = 6.0, rhamnose CH_3) [64]
Biological activity: antimicrobial [37]



29. Forsythiaside

Syringa vulgaris L. (bark), Oleaceae [64]; *Digitalis purpurea* L. (callus culture of leaves), Scrophulariaceae [75]; *Calceolaria ascendens* (herb), Scrophulariaceae [11]; *Rhemania glutinosa* (callus culture), Scrophulariaceae [77]; *Forsythia suspensa* Vahl. (fruit and leaves), Oleaceae [78]

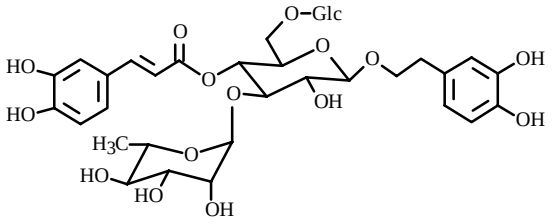
$C_{29}H_{36}O_{15}\cdot H_2O$
mp: 147-150°C (H_2O)
$[\alpha]_D$ -17.8° (CH_3OH)
UV: 235, 242, 298 sh, 330 nm
Mass (270°): 316 (13), 180, 163, 154 (52), 137 (49), 136 (35), 123 (100)
PMR (C_5D_5N, 100 MHz, ppm, J/Hz): 8.00 (1H, d, J = 16.0, H-7‴″), 6.7-7.2 (4H, m, H-Ar), 6.67 (1H, d, J = 16.0, H-8‴″), 6.20 (2H, br.s, H-2, H-2′), 5.62 (1H, br.s, H-1‴), 5.52 (1H, t, J = 10.0, H-4″), 4.80 (1H, d, J = 7.0, H-1″), 3.7-4.8 (12H, m, 2H-8 and 10H of sugars), 2.88 (2H, t, J = 7.0, H-7), 1.58 (3H, d, J = 6.0, rhamnose CH_3) [64]
Biological activity: antimicrobial [37]



30. Forsythoside C

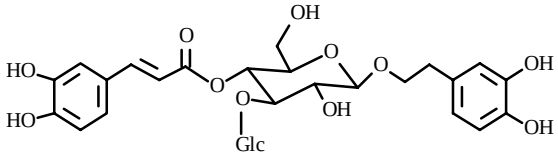
Forsythia suspensa Vahl. (fruit), Oleaceae [79]
$C_{29}H_{36}O_{16}$, amorphous substance
$[\alpha]_D^{18}$ -18.7° (CH_3OH)

UV: 219, 245, 290, 302, 332 nm
Biological activity: antimicrobial [37, 75]



31. Echinacoside

Echinacea angustifolia Moench. (roots), Asteraceae [11, 40]; *Syringa reticulata* (Blume) Hara (leaves), Oleaceae [80]
$C_{35}H_{46}O_{20}\cdot 4H_2O$
$[\alpha]_D$ -56.5° (H_2O)
Biological activity: antimicrobial [37]



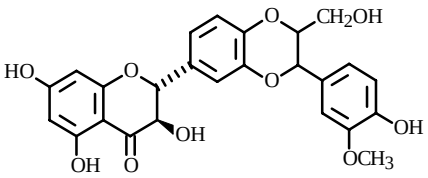
32. Plantamajoside

Plantago major L. subsp. Major (leaves), Plantaginaceae [100]
$C_{29}H_{36}O_{16}$, amorphous substance
$[\alpha]_D^{19.2}$ -42.47° (CH_3OH)
UV: 220, 247, 292, 332 nm

IR: 3350, 1685, 1625, 1600
PMR ($CDCl_3$, 90 MHz, ppm, J/Hz): 7.03 (1H, dd, J = 2.0, J = 10.0, H-6‴″), 6.68 (1H, d, J = 10.0, H-5‴″), 6.72 (1H, d, J = 9.0, H-6), 6.65 (1H, d, J = 10.0, H-5), 6.52 (1H, d, J = 2.0, H-2), 7.61 (1H, d, J = 16.0, H-7‴″), 6.34 (1H, d, J = 16.0, H-8‴″), 4.59 (1H, d, J = 12.0, H-1, glucose), 4.45 (1H, d, J = 12.0, glucose H-1), 3.80 (2H, t, J = 7.0, H-8), 2.88 (2H, d, J = 7.0, H-7) [100]
Biological activity: antimicrobial [100]

LIGNOIDS (OXIDATIVE COUPLING PRODUCTS OF PHENYLPROPANOIDS)

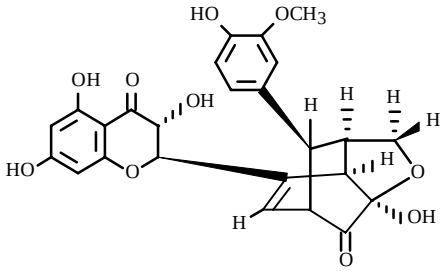
FLAVOLIGNANS



33. Silybin

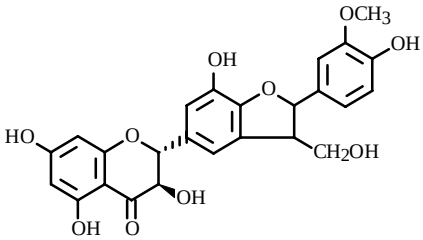
Silybum marianum (L.) Gaertn. (fruit), Asteraceae [81]
$C_{25}H_{22}O_{10}$
mp: 164-168°C
$[\alpha]_D$ +10.8° (acetone)
UV: 289, 325 (sh) nm

Mass: 482 (70), 464 (26), 302 (5), 180 (96), 162 (28), 137 (100), 124 (57)
PMR (CD_3COCD_3, 50°, 200 MHz): 11.70 (1H, s, 5-OH), 6.8-7.2 (6H, m, H-Ar), 5.96 (2H, d, J = 2.0, H-6, H-8), 5.10 (1H, d, J = 12.0, H-2), 5.00 (1H, d, J = 8.0, H-7″), 4.60 (1H, d, J = 12.0, H-3), 4.1-4.2 (1H, m, H-8″), 3.3-3.8 (2H, m, H-9″), 3.85 (3H, s, OCH_3) [83]
Biological activity: hepatoprotector [37, 154]



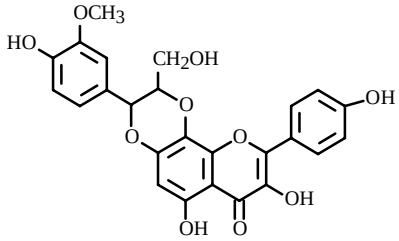
34. Silydianin

Silybum marianum (L.) Gaertn. (fruit), Asteraceae [7]
$C_{25}H_{22}O_{10}$
mp: 174-175°C
$[\alpha]_D$ +81.4° (pyridine)
UV: 288, 322 (sh) nm
Mass: 482 (3), 464 (2), 302 (14), 180 (44), 137 (54), 124 (28)
PMR (CD_3COCD_3, 200 MHz, J/Hz): 11.76 (1H, s, 5-OH), 9.78 (1H, br.s, 7-OH), 6.7-7.0 (3H, m, H-Ar), 6.30 (1H, m, H-6′), 6.02 (2H, br.s, H-6, H-8), 4.92 (1H, dd, J = 12.0, J = 2.0, H-2), 4.65 (1H, dd, J = 12.0, J = 3.0, H-3), 4.29 (1H, dd, J = 8.0, J = 3.5, H-9″), 3.78 (1H, d, J = 8.0, H-9″), 3.75 (3H, s, CH_30), 3.66 (1H, dd, J = 4.0, J = 2.0, H-2′), 3.42 (1H, m, H-7″), 3.28 (1H, dd, J = 6.0, J = 2.5, H-5′), 2.9 (1H, m, H-8″) [83]
Biological activity: hepatoprotector [37, 154]



35. Silychristin

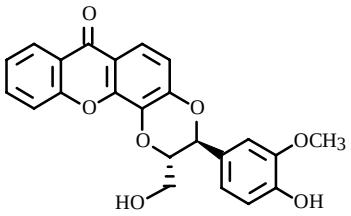
Silybum marianum (L.) Gaertn. (fruit), Asteraceae [7]
$C_{25}H_{22}O_9$
mp: 189-191°C
$[\alpha]_D$ +218.0° (pyridine)
UV: 288, 325 (sh) nm
Mass: 482 (19), 464 (47), 137 (45)
PMR (CD_3COCD_3, 200 MHz, J/Hz): 1.86 (1H, s, 5-OH), 6.8-7.18 (6H, m, H-Ar), 6.0 (1H, d, J = 2.0, H-8), 5.96 (1H, d, J = 2.0, H-6), 5.60 (1H, d, J = 6.4, H-7″), 5.05 (1H, d, J = 11.5, H-2), 4.65 (1H, d, J = 11.5, H-3), 4.1-4.3 (1H, m, H-8″), 3.5-3.8 (2H, m, H-9″), 3.82 (3H, s, CH_3O) [83]
Biological activity: hepatoprotector [37, 154]



36. Rhodiolin

Rhodiola rosea L. (rhizome) [23]; *R. arctica* Boriss. (rhizome), Crassulaceae [56]
$C_{25}H_{20}O_{10}$ (M^+ 480)
mp: 235-237°C (ethanol)
$[\alpha]_D$ ±0° (acetone)
UV: 230, 260, 281, 382 nm
Mass: 480 (16), 462 (1), 302 (100), 180 (56), 151 (17), 137 (88), 124 (48)
PMR (CD_3COCD_3, 100 MHz, J/Hz): 11.6 (1H, s, 5-OH), 8.24 (2H, d, J = 9.0, H-2′, H-6′), 7.17 (1H, d, J = 2.0, H-2″), 7.04 (1H, dd, J = 2.0, J = 9.0, H-6″), 7.00 (2H, d, J = 9.0, H-3′, H-5′), 6.94 (1H, d, J = 8.0, H-5″), 6.32 (1H, s, H-3), 5.27 (1H, d, J = 8.0, H-7″), 4.23 (1H, m, H-8″), 4.00 (1H, dd, J = 3.0, J = 12.0, H-9″), 3.88 (3H, s, CH_3O), 3.66 (1H, dd, J = 4.0, J = 12.0, H-9″) [23]

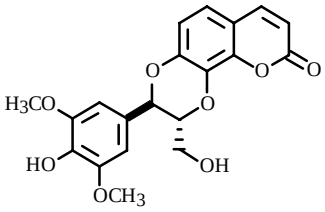
XANTHONOLIGNANS



37. Kielcorin

Kielmeyera coriacea (roots) [84]; *Hypericum refluxum* L. (herb), Hypericaceae [85, 86]; *Psorospermum febrifigum* [87]
$C_{24}H_{20}O_8$
mp: 189-191°C
$[\alpha]_D$ +218.0° (pyridine)
UV: 288, 325 (sh) nm

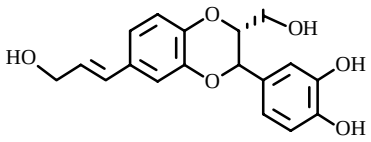
COUMARINOLIGNANS



38. Daphneticin (revised structure)

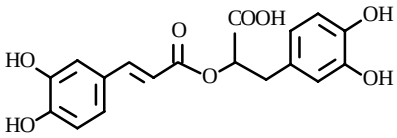
Daphne tangutica (stems and roots), Thymelaeaceae [50]
$C_{20}H_{18}O_8$
$[\alpha]_D$ ±0° (pyridine)
mp: 235-238°C
UV: 242, 260, 317 nm
IR: 3450, 1720, 1610, 1565
Mass: 386 (100) $[M]^+$, 354, 311, 219, 210, 178, 167, 150
PMR (DMSO-d_6, 100 MHz, J/Hz): 8.55 (1H, br.s, OH), 7.96 (1H, d, J = 9.5, H-4), 7.18 (1H, d, J = 9.0, H-5), 6.94 (1H, d, J = 9.0, H-6), 6.75 (2H, s, H-2′, H-6′), 6.31 (1H, J = 9.5, H-3), 5.03 (1H, d, J = 8.0, H-7′), 4.32 (1H, m, H-8′), 3.78 (3H, s, each 2×OCH_3), 3.48 (2H, m, H-9′) [207]
Biological activity: anticancer activity [37, 207]

NEOLIGNANS



39. Americanol A

Phytolacca americana L. (fruit), Phytolaccaceae [88]
$C_{18}H_{18}O_6$ (M^+ 330)
mp: 125-128°C (ethylacetate—acetone)
$[\alpha]_D^{27}$ ±0°
UV: 260, 268, 300, 312 nm
Biological activity: hepatoprotector [37], neutropic activity [143]

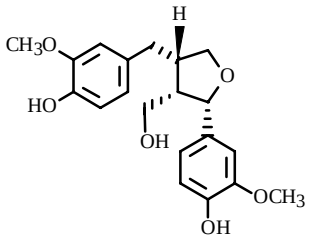


40. Rosmarinic acid

Rosmarinus officinalis L. (leaves), Lamiaceae [41]; *Melissa officinalis* L. (leaves, herb), Lamiaceae [12, 60] and other plants [89]
$C_{18}H_{16}O_8$
mp: 204°C (dec.)
$[\alpha]_D^{20}$ +145° (ethanol)
UV: 242, 290, 327 nm

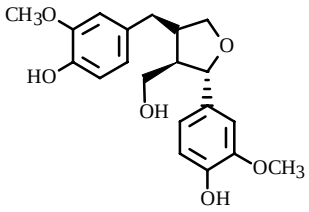
PMR (CD_3COCD_3, 100 MHz, ppm, J/Hz): 7.54 (1H, d, J = 16.0, H-7), 6.5-7.2 (6H, m, H-Ar), 6.26 (1H, d, J = 16.0, H-8), 5.22 (1H, q, J = 4.0, J = 7.0, H-8′), 3.06 (1H, t, J = 7.0, H-7′) [41]
Biological activity: antiviral and immunomodulating activities [12, 37]

LIGNANS (PHENYLPROPANOID DIMERS)



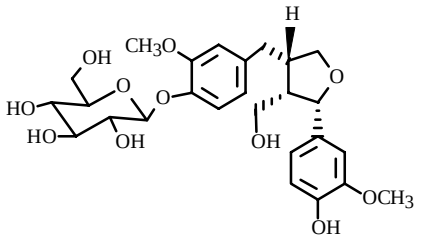
41. (-)-Lariciresinol

Rhodiola rosea L. (tissue culture) [25, 90]; *Dirca occidentalis* A. Gray (flowers and branches), Thymelaeaceae [70]
$C_{20}H_{24}O_7$ (M^+ 360), syrupy substance
$[\alpha]_D^{23}$ -24.2° (ethanol)
UV: 230, 282 nm [25, 90]
mp: 160-162°C
$[\alpha]_D^{17}$ -17.8° (acetone)
UV: 232, 282 nm [70]
Mass: 360 (17) $[M]^+$, 151 (100), 137 (62)
Biological activity: anticancer activity [37]



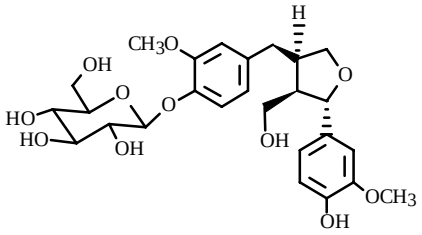
42. (+)-Lariciresinol

Wikstroemia elliptica Merill. (stem bark), Thymelaeaceae [70]
$C_{20}H_{24}O_7$
mp: 168°C
$[\alpha]_D^{17}$ +19.7° (acetone)
UV: 230, 282 nm [25, 90]
Mass: 360 (100) $[M]^+$, 194 (23), 180 (19), 175 (16), 153 (23), 151 (52), 150 (18), 137 (90)
Biological activity: anticancer activity [37]



43. (-)-Lariciresinol 4-O-β-D-glucopyranoside

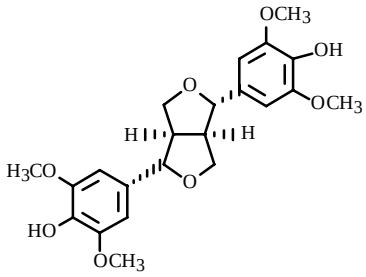
Rhodiola rosea L. (tissue culture) [25, 70]
$C_{26}H_{34}O_{11}$, amorphous substance
$[\alpha]_D^{20}$ -25.9° (ethanol)
UV: 227, 280 nm
PMR (C_5D_5N, 250 MHz, ppm, J/Hz): 7.53 (1H, d, J = 8.7, H-5′), 7.25 (1H, d, J = 2.0, H-2′), 7.14 (1H, d, J = 8.7, H-5), 7.08 (1H, dd, J = 8.7, J = 2.0, H-6′), 6.93 (1H, d, J = 2.0, H-2), 6.82 (1H, dd, J = 8.7, J = 2.0, H-6), 5.63 (1H, d, J = 6.5, H-1″), 5.27 (1H, d, J = 6.0, H-7″), 4.47 (1H, dd, J = 12.0, J = 2.0, H-6″), 3.9-4.4 (9H, m, 5H of glucose + 2H-9 + 2H-9′), 3.70 (3H, s, CH_3O), 3.60 (3H, s, CH_3O), 3.17 (1H′, dd, J = 5.0, J = 14.0, H-7), 2.95 (1H, m, H-8), 2.7 (2H, m, H-7, H-8′) [25]



44. (+)-Laricіresinol 4-O-β-D-glucopyranoside

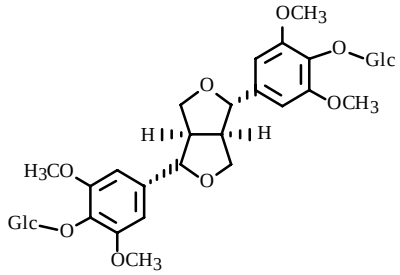
Syringa vulgaris L. (bark), Oleaceae [92]
$C_{26}H_{34}O_{11}$, amorphous
$[\alpha]_D^{19}$ +18.2° (ethanol)
UV: 227, 282 nm

PMR (C_5D_5N, 250 MHz, ppm, J/Hz): 7.53 (1H, d, J = 8.7, H-5′), 7.25 (1H, d, J = 2.0, H-2′), 7.14 (1H, d, J = 8.7, H-5), 7.08 (1H, dd, J = 8.7, J = 2.0, H-6′), 6.93 (1H, dd, J = 2.0, H-2), 6.82 (1H, dd, J = 8.7, J = 2.0, H-6), 5.63 (1H, d, J = 6.5, H-1″), 5.27 (1H, d, J = 6.0, H-7″), 4.47 (1H, dd, J = 12.0, J = 2.0, H-6″), 3.9-4.4 (9H, m, 5H of glucose + 2H-9 + 2H-9′), 3.70 (3H, s, CH_3O), 3.60 (3H, s, CH_3O), 3.17 (1H, dd, J = 5.0, J = 14.0, H-7), 2.95 (1H, m, H-8′), 2.7 (2H, m, H-7, H-8′) [25]



45. Syringaresinol

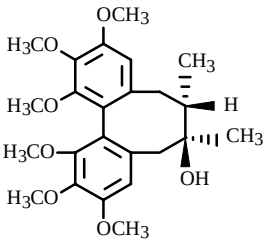
Eleutheroococcus senticosus (Rupr. et Maxim.) Maxim. (roots), Araliaceae [19]
$C_{22}H_{26}O_8$ (M^+ 418), amorphous substance
UV: 237, 273 nm
Mass (200°): 418 (69) $[M]^+$, 210 (19), 193 (44), 183 (25), 182 (81), 180 (25), 168 (28), 167 (90), 161 (40), 154 (13), 149 (44), 91 (8) [19]



46. Eleutheroside D (Syringaresinol-4,4′-O-diglucopyranoside)

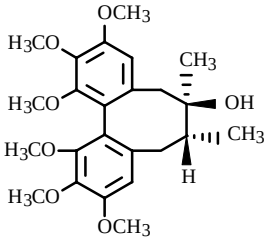
Eleutherococcus senticosus (roots), Araliaceae [19, 68]; *Eleutherococcus senticosus* (roots), Araliaceae [19]; *Eleutherococcus senticosus* (roots, bark) [92]
$C_{34}H_{46}O_{18}$
mp: 255-257°C [19, 92]
UV: 234, 271 nm
$[\alpha]_D^{23}$ -6.1° (50% ethanol) [19, 92]

mp: 247°C
$[\alpha]_D^{20}$ -31.2° (pyridine)
UV: 234, 271 nm [68]
Mass (220°): 418 (73), 210 (13), 183 (17), 182 (40), 181 (100), 180 (100), 168 (17), 167 (70), 154 (17), 153 (17), 152 (83), 151 (40) [19]
PMR (DMSO-d_6, 200 MHz, ppm, J/Hz): 6.65 (4H, s, H-2,6 and H-2′,6′), 5.03 (4H, br.s, 2H-9, 2H-9′), 4.95 (d, 7 Hz, H-1″, H-1‴), 4.90 (2H, d, 8 Hz, H-7, H-7, H-7′), 4.68 (2H, m, 2H of glucose), 4.33 (1H, t, 6 Hz, H-8), 4.20 (1H, t, 6 Hz, H-8′), 3.82 (12H, s, 4 CH_3O), 3.0-3.9 (10H of glucose) [19]
Biological activity: tonic [37]



47. Schizandrin

Schizandra chinensis Bail. (fruit), Schizandraceae [93]
$C_{23}H_{28}O_6$
mp: 93-95°C
UV: 220.5, 254, 282 nm [93]
Biological activity: tonic [37]



48. Isoschizandrin

Schizandra chinensis Bail. (fruit), Schizandraceae [93]
$C_{24}H_{32}O_7$ (M^+ 432), amorphous substance
$[\alpha]_D^{20}$ +92° ($CHCl_3$)
UV: 218, 251, 284 nm [93]
Biological activity: tonic [37]

3. ISOLATION AND PURIFICATION OF PHENYLPROPANOIDS

Isolation and purification of phenylpropanoids require a separate examination because many phenylpropanoids, especially lignan glycosides and conjugates of phenylethanoids, are noncrystalline compounds. Therefore, additional effort is needed to isolate them. Apparently for this reason many phenylpropanoids that were recently isolated [45, 46, 50, 51, 90, 94, 95] were not investigated for a long time.

Refined preparative methods of isolation, including high-pressure liquid chromatography (HPLC), made success in this area possible. It should be emphasized that many phenylpropanoid glycosides were isolated using preparative HPLC [9, 10, 45, 77, 81, 96-99].

Favorable extraction conditions, evaporation methods, and other technical operations are advisable for isolating phenylpropanoids in the native state [9, 77, 81, 100]. In certain instances, isolation of phenylpropanoids is so difficult that they can be obtained only after chemical modification, in particular, acetylation [69]. Sorbents that are used most often are silica gel, cellulose, and Sephadex LH-20. The majority of phenylpropanoids was purified using the last sorbent [9, 10, 20, 96-98]. It is interesting that noncrystalline cinnamyl glycosides of roseroot rhizome, rosarin and rosin, could be isolated and purified only if Sephadex LH-20 was used [20]. In our opinion, the rare usage of polyamide to isolate phenylpropanoids is unjustified. We used this sorbent (Woelm, Germany) to isolate phenylpropanoids from rhizome and tissue-culture biomass of roseroot, arctic rhodiola rhizome, common lilac bark, and medicinal melissa [20, 25, 56-58, 60, 92, 101].

Fractionation by various organic solvents is also effective for separating phenylpropanoids [10, 74, 96-98].

We proposed new methodic approaches to the isolation of phenylpropanoids and other natural compounds from plant material based on research results. These include the use of column chromatography with thin (3-5 cm) sorbent layers. It was shown that the amount of separated mixture is controlled not by the height of the sorbent layer (using silica gel and polyamide as examples) but the column diameter [27, 100].

The proposed approach was used to prepare four State Standard Samples (GSO) of syringin (eleutheroside B), rosavin, triandrin, and silybin [2, 27, 31, 33, 36, 91, 101, 102].

4. STRUCTURAL ANALYSIS OF PHENYLPROPANOIDS. DEPENDENCE OF SPECTRAL AND CHEMICAL PROPERTIES ON PHENYLPROPANOID STRUCTURE

Structural analysis of phenylpropanoid glycosides is rapidly developing. However, this area has not yet been reviewed.

We attempted to systematize and review the literature and our own research results on structural analysis of phenylpropanoids. In this section, structural analysis of lignans and other lignoids is not reviewed because these topics have been discussed in detail in the literature, including one of our reviews [3]. Structural investigations of lignoids has developed rather successfully over the last 10-15 years. Thus, certain structures of natural xanthonolignans (**37**) and coumarinolignans (**38**, Table 2) were confirmed or revised using synthesis or heteronuclear magnetic resonance spectroscopy [50, 103-107].

All chemical and spectral methods that are used to establish structures of natural compounds are also used in structural investigations of phenylpropanoids.

Nuclear magnetic resonance (NMR) is the most informative method. Proton magnetic resonance (PMR) spectra of glycosides containing cinnamic acid derivatives exhibit characteristic doublets for protons of the side chain (–CH=CH–) with a spin—spin coupling constant (SSCC) of 16 Hz (the chemical shift of H-7 is 7.5-8.0 ppm; of H-8, 6.2-6.5 ppm) [9, 25, 27, 77, etc.].

Comparison of PMR spectra of starting glycosides and their acetates can reveal aromatic and aliphatic OH groups (singlets of aromatic acetoxyls resonate at weaker field) and the structure of the carbohydrate moiety [20, 23, 25, 29, 30, 36].

A 3H singlet at 3.8-4.0 ppm is observed in the PMR if the glycoside contains an aromatic methoxyl [23, 50, 52].

Signals of the 2H-α^1 (on C-8) and 2H-β^1 (on C-7) protons are diagnostic for the phenylethanol fragment. These appear in the PMR as two 2H triplets with SSCC 7 Hz (2.83 and 3.95 ppm, respectively) [37, 64, 77, 109].

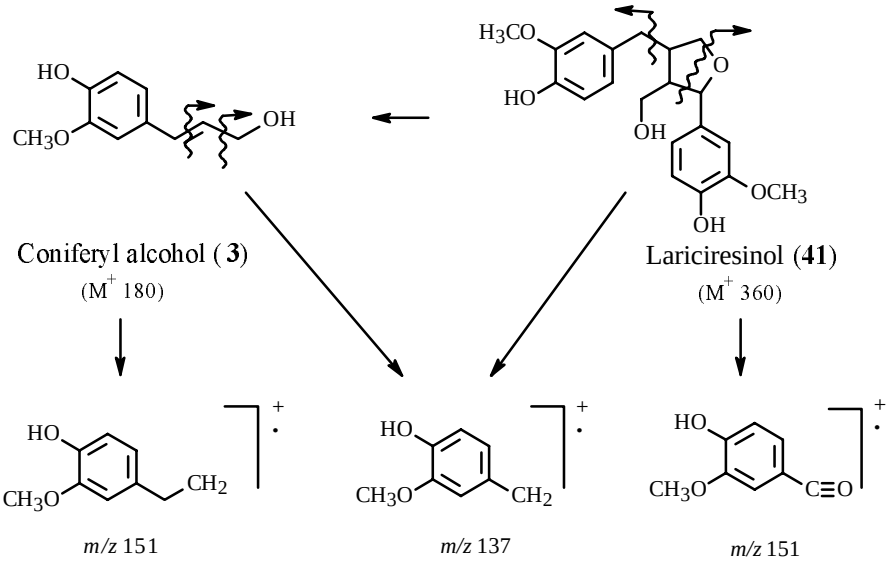
The signals of the cinnamyl and phenylethyl aromatic protons are affected by the substituents. In particular, the aromatic protons in *p*-substituted structures resonate as two 2H doublets with SSCC 9 Hz (H-2,6; H-3,5) [25, 49, 109].

^{13}C NMR has been used successfully for structural analysis of phenylpropanoids, especially for establishing the structure of the carbohydrate [10, 94, 110, 111, etc.] and for determining the site of attachment of the cinnamic acid. Thus, attachment of rhamnose to the OH on C-3 in campneoside [111] was established based on the fact that the glucose C-3 signal in the NMR undergoes a paramagnetic shift (+3.1 ppm) (glycosylation effect). Furthermore, systematic studies of lignoids by ^{13}C NMR spectroscopy [3, 37, 207, 208] showed that compounds with 1,4-dioxane and 2,3-dihydrofuran structures are differentiated by this method. In particular, the signals of C-7 (C-α), C-8 (C-β), and C-9 (C-γ) in all 1,4-dioxanes (for example, lignoids) differ substantially from those of the corresponding dihydrobenzofurans, for example, compounds with spectra in which C-8 and C-9 (–CH_2OH) appear at weaker field (+10-15 and +2-3 ppm, respectively); C-7, at stronger field (-30 ppm). The chemical shifts of this group have special diagnostic value for determining the configuration and conformation of the molecule [3, 37, 207, 208]. It is also important to note that double (^{13}C–^{1}H)-heteronuclear magnetic resonance can be used to determine the isomerism of the substituent positions in the 1,4-dioxane fragment of cleomiscosin A [208]. Thus, the structure of this coumarinolignan was established based on the presence in the spectrum of its diacetate of (^{13}C–H^1)-spin heterodecoupling between the signals of C-7 (δ 136.9) and H-8 (δ 4.1 ppm) and of C-8 (δ 135.5) and H-7 (δ 5.03 ppm) [208]. The structure of another coumarinolignan, daphneticin, was determined analogously [207].

Mass spectrometry is also useful in structural studies of phenylpropanoids. It should be noted that the molecular ion $[M]^+$ of phenylpropanoid glycosides can appear only if field-desorption mass spectrometry (FD-MS) or fast-atom-bombardment mass spectrometry (FAB-MS) is used. For example, the peak for the ion with *m*/*z* 593 $[M + H]^+$ is consistent with the empirical formula $C_{29}H_{36}O_{13}$ in the mass spectrum of jionoside C [77].

Electron-impact mass spectrometry (EI-MS) was used to study phenylpropanoid glycosides and could detect characteristic fragments [37, 64]. Thus, the mass spectrum of acteoside (**28**) exhibits diagnostic fragments of the hydroxyphenylethyl alcohol, i.e., strong peaks for ions with *m*/*z* 154, 137, 135, and 123, respectively.

EI-MS was also used to study compounds containing cinnamyl alcohols [3, 20, 25, 108, 110, 112]. Thus, cinnamylglycosides **11**-**17** and lignoids **33**-**36** [3, 20, 25, 53, 54, 60] exhibit strong peaks for the molecular ions of the cinnamyl alcohols and their fragmentation products (*m*/*z* 137 and 151 for coniferyl alcohol). For lignans, it was noted that a strong peak for the benzoyl ion with *m*/*z* 151 is formed in addition to that of benzyl (*m*/*z* 137) in the mass spectrum of lariciresinol (**41**) [25, 110].



Scheme 1. Mass spectrometrical fragmentation of phenylpropanoids **3** and **41**.

IR and UV spectroscopies are also used for structural investigations of phenylpropanoids (Scheme 1). IR spectra of phenylpropanoids containing an ester have a characteristic absorption band at ~1700 cm^{-1} (C=O) [34, 47, 133, 171-174, 112, etc.]. IR spectra of cinnamoylamides contain absorption bands near 1750 cm^{-1} (amide C=O) [37, 89, 113].

UV spectra of phenylpropanoids are also rather characteristic and enable the nature of the compounds to be determined. Thus, UV spectra of **18**-**24** and **28**-**32**, which contain hydroxycinnamic acids, have practically the same absorption maxima as the free hydroxycinnamic acids (e.g., 227, 242, 290, and 330 nm for the caffeates) [1, 25, 58, 64, 75].

Strong absorption maxima at 250-280 nm are characteristic of the UV spectra of cinnamyl alcohols **1**-**4**; lignans **41**, **45**, **47**, and **48**; and their glycosides **43**, **44**, and **46** [19, 25, 59, 67].

Chemical methods, especially enzymatic and acid and base hydrolysis, are used to establish the structure of phenylpropanoids. Under strong-acid hydrolysis conditions, phenylpropanoid glycosides, in particular, mussatioside I [109], is cleaved and forms the corresponding cinnamic acid, sugar (glucose, rhamnose, xylose), and hydroxyphenylethyl alcohol; under mild-acid hydrolysis (0.5% HCl), mussatioside I dexyloside and xylose. Base saponification cleaves cinnamic acid and produces the deacylated analog of mussatioside I [109]. Chemical reactions in combination with acetylation and methylation [109, 110] can establish the attachment site of the substituent and the order of sugar attachment. Enzymatic hydrolysis by β-glucosidase, the gentlest cleavage method, is widely used to study cinnamyl-alcohol glycosides and lignans because the aglycon under acid-hydrolysis conditions, as a rule, is decomposed [20, 25, 37, 64].

We discovered several features of the spectral and chemical properties of phenylpropanoids during structural investigations [27]. We found that the signal of the anomeric proton of the glucose bound to the aromatic hydroxyl is shifted to weak field (by 0.5-0.8 ppm) in the PMR spectra of coniferin (**16**), syringin (**17**), and other glycosides compared with the signal of the anomeric proton of the carbohydrate of compounds [rosin (**11**), rosavin (**12**), rosarin (**13**), triandrin (**14**)] that have a glycosylated alcohol OH.

The PMR spectra of hydroxycinnamic-acid glycosides **20**-**23** showed [27] that the signal of the anomeric proton of the glucose bound to the carboxyl is observed at weaker field (by 0.8-1.0 ppm) than that of the glucose bound to the aromatic hydroxyl of these phenylpropanoids.

These features can be used for structural analysis of not only phenylpropanoids but also other natural compounds.

The results of our biosynthetic investigations are also interesting [114]. Using oxidative coupling of previously isolated herbacetin (3,5,7,8,4′-pentahydroxyflavone) and the corresponding cinnamyl alcohols **2**-**4** in the presence of peroxidase (Fluka, Hungary), we prepared flavolignans rhodiolin (**35**), demethoxyrhodiolin, and methoxyrhodiolin [114]. Further investigations synthesized flavoconiferin and flavosyringin [37] from bitalogenin (5,6,7,8,3′,4′-hexahydroxyflavone) isolated from flowers of Italian everlasting [1].

It is important to emphasize that rhodiolin (**35**) was previously isolated from roseroot rhizomes and arctic rhodiola [23, 56, 115]. Flavolignans demethoxyrhodiolin and methoxyrhodiolin are new natural compounds. It was established during the

research that the reactivity of the phenylpropanoids increases in the order: cinnamyl alcohol (**1**) < *p*-coumaryl alcohol (**2**) < coniferyl alcohol (**3**) < sinapyl alcohol (**4**). This trend explains why coniferyl and sinapyl alcohols play the leading role in the boisynthesis of lignans, neolignans, and lignoids (including **33**-**36** and **42**-**46**), which are widely distributed in plants.

Considering that cinnamyl alcohol under these experimental conditions was unreactive, occurrence in plants of any products of oxidative coupling of this compound can hardly be expected in the future. Synthesis of methoxyrhodiolin can be expected in plants with a chemical makeup similar to that of roseroot, arctic rhodiola, and other plants containing herbacetin.

Flavolignans (flavolignans and flavonolignans) are flavonoids that contain an additional C_6-C_3 fragment (basically a coniferyl alcohol moiety). They represent a comparatively sparse new group of natural compounds [3, 5-7, 37, 45, 82, 83, 110, 112, 116-119]. This provides a basis for assigning flavolignans to not only flavonoids but also phenylpropanoids [3, 58, 120, 121]. The first representative of flavolignans was silybin (**33**), which was isolated from fruit of variegated milk-thistle. More than 20 years was needed to solve the chemical structure of this compound owing to the unusual characteristics [3, 37, 112, 117-119, 122, 123]. German scientists dealt the decisive blow to solving this conundrum by proving the chemical structure using PMR, ^{13}C NMR, UV and IR spectroscopies, and mass spectrometry in combination with chemical methods [7, 19, 99, 123-129].

It is noteworthy that the published methodic and methodologic material on the structural investigation of silybin as a representative of a new class of natural compounds fostered success in the study of the chemical structure of flavolignans. Further investigations isolated from fruit of variegated milk-thistle silydianin (**34**) and silychristin (**35**) [37, 124], which belong along with silybin to the dominant flavolignans, and several flavolignans of flavanonolic, flavanonic, and flavonolic nature [3, 23, 37, 83, 98, 99, 124-131].

5. PHARMACOLOGIC PROPERTIES OF PHENYLPROPANOIDS

Tonics of roseroot, thorny eleutherococcus root, Chinese lemon seed, and other plants are used effectively in medical practice [4, 18, 37, 42, 68, 93, 113, 132-134].

Glycosides of cinnamyl alcohol, which are dominated by rosavin (**12**) [14-16, 24, 37, 132, 135, 136], are responsible for the biological activity of roseroot rhizome. The second group of active compounds in this plant material consists of simple phenols such as tyrosol and salidroside [15, 16, 132, 136].

In our opinion, the stimulatory and adaptogenic properties of callus and suspension culture of roseroot [71, 137, 138] are due to triandrin (**14**) and other phenylpropanoids [14, 16, 25, 136]. Triandrin is a hydroxylated analog of rosin (**11**) that is isolated from roseroot rhizome [20].

The biological activity of thorny eleutherococcus preparations is due to the sinapyl-alcohol glycoside syringin (eleutheroside B) (**17**) and the diglucoside of the lignan syringaresinol, eleutheroside D (E) (**46**) [16-18, 136, 139, 140].

It can be assumed that the stimulatory properties of Chinese lemon preparations [88] are also due to lignans described for this plant [41, 93, 141, 142]. These include schizandrin (**47**) and isoschizandrin (**48**), although this plant material has until now been standardized without accounting for the active principles. Neutron activation was also performed for americanol A (**39**) and isoamericanol A [143], which are members of the populous neolignan group [45, 59, 120, 144].

Anticancer activities of preparations of roseroot [145-147], thorny eleutherococcus [139, 140], and white mistletoe [99] are also probably due to phenylpropanoids because distinct immunostimulating properties have been observed for eleutheroside B and syringaresinol (**45**) [90, 140]. Anticancer properties were also found for another lignan, lariciresinol (**42**) [70, 90, 149] and its various derivatives [70, 146, 149]. This suggests that anticancer properties will be found for tissue-culture biomass of roseroot, from which we isolated lariciresinol (**41**) and its new 4-glucoside (**43**) [25, 57].

The bark of common lilac is also interesting. We isolated from it the stereoisomer of **43**, (+)-lariciresinol 4-O-glucoside (**44**) [92]. Plants of the Pinaceae family may also be promising sources of anticancer preparations. Lariciresinol and its various derivatives are found in them [146, 149].

Anticancer activity is also characteristic of lignoids such as the coumarinolignans daphneticin (**38**) and cleomiscosin A and B [70, 136, 145].

We isolated several phenylpropanoids (**1** and **2**) and their glycosides (**11**-**14**, **17**) during an investigation of the chemical composition of medicinal plants such as roseroot (rhizome and tissue culture), thorny eleutherococcus, common lilac, and basket willow [27, 37]. We also studied the biological activity [14-16, 136].

Comparison of the spontaneous motor activity of mice in an actograph showed that the stimulating activity of

phenylpropanoids at doses of 10 mg/kg increases in the order syringin (**17**) < rosavin (**12**) < triandrin (**14**). At doses of 50 mg/kg, rosavin has the highest stimulating properties. Its activity increases constantly over a period of 90 min (44.2% relative to a control) whereas triandrin and syringin have a distinct stimulating effect for the first 30 min.

We investigated the neurotropic activity of the compounds using a chloral-hydrate sleep model and found that triandrin and rosavin and to a lesser extent syringin exhibit stimulating properties [15, 16]. Administration of *p*-coumaryl alcohol (**2**) produced no excitatory effect whereas administration of cinnamyl alcohol (**1**) produced only a tendency to shorten the chloral-hydrate sleep. For sodium-barbital sleep [16], syringin had the highest stimulating activity. The activities of the other compounds, including aglycons (**1** and **2**), were lower.

Thus, a study of the antihypnotic properties of phenylprpanoids [14-16, 136] showed that triandrin and rosavin elicit an excitatory effect by affecting the brain cortex (chloral-hydrate sleep model); syringin, the subcortical brain structures (sodium-barbital sleep). A comparison of the neurotropic properties of glycosides **12**-**14** and **17** and their aglycons **1** and **2** found that phenylpropanoids with a glycosylated –CH=CH–CH_2–OH group (**11**-**14**) have significantly higher stimulating activity than their aglycons cinnamic **(1)** and *p*-coumaryl **(2)** alcohols [16, 136].

Immunostimulating properties of **12**, **14**, and **17** were studied [136]. Syringin (**17**) had the highest immunostimulating activity (119% relative to a control); rosavin (**12**), high activity (49%). It is interesting that the neurotropic activity in this series of compounds increases such that triandrin (**14**) is the most active, in contrast with the immunostimulating properties.

Pharmacological properties of cinnamylglycosides indicate that this area holds much promise. Rutinosides of cinnamyl alcohol, which is isolated from quaking aspen (*Populus tremula* L.) bark, are definitely interesting [95].

Immunostimulating properties of other phenylpropanoids deserve attention. In particular, cichoric acid (**24**) and its various derivatives in addition to polysaccharides [10, 150, 151] are responsible for the immunostimulating and antiviral properties of purple echinacea preparations, one of the most popular medicinal plants of modern medicine [35, 37, 39, 148, 151]. The literature on the anticancer activity of acteoside (**28**) and isoacteoside [76] is very interesting because **28** is widely distributed in plants. Furthermore, the immunsuppressive properties of acteoside, purpureaside C, echinacoside (**31**), cistanosides, and other phenylpropanoid glycosides [77] in addition to the antistress activity of cistanosides [96-98] have been described.

Flavolignans of variegated milk-thistle fruit are unique [6, 7, 116]. These compounds differ fundamentally from known flavonoids [6]. Silybin (**33**), silydianin (**34**), and silychristin (**35**) (the mixture of these compounds is called silymarin) are most interesting with respect to biological activity. They have a unique hepatoprotective activity [6, 7, 107, 108, 112] and are used in structural, analytical, technical, pharmacological, toxicological, and clinical investigations. Fruit of variegated milk-thistle cultivated in Samara district afforded **33**, **34**, and **35** and 2,3-dehydrosilybin, which was first described by us for this plant cultivated in Russia and the CIS [152, 153].

An important property of the total flavolignans **33**, **34**, and **35** is the ability to exert protective and curative effects during galactosamine intoxication, the pathogenesis of which is reminiscent of the morphlogical changes induced by hepatitis virus in man [6]. A comparison of the antihepatotoxic properties of the flavolignans showed [6, 7, 107, 116, 154] that **34** and silymonin are most active for the galactosamine models whereas **33**, silandrin, silyhermin, and silymonin exhibited the highest effects for CCl_4 models. This led to the conclusion that 3-deoxyflavolignans possess the highest heptoprotective activities [116].

An especially valuable property of silimarin (total flavolignans) is its ability to neutralize the action of the very strong liver toxins phalloidin and α-amanitin, which are found in the destroying angel mushroom [6]. Administration of silymarin protects 100% of mice from poisoning by its toxins (3 mg/kg) [6]. An analogous effect was observed after administration of silybin not later than 20 min after poisoning animals. The time factor is considered [6] to be very important because phalloidin and α-amanitin have different mechanisms of action. Phalloidin destroys the external membranes of liver cells and leads to death after several hours whereas α-amanitin penetrates into cell nuclei and suppresses protein synthesis, which leads to death in 3-5 days. Therefore, an effective treatment plan was proposed for people poisoned with toxins from the destroying angel [6].

The new flavolignans salcolin A and B were relatively recently isolated from the aerial part of the tumbleweed *Salsola collina* Pall. (Chenopodiaceae) [130]. A preparation with hepatoprotective properties was developed based on them [37]. Other lignoids such as the neolignan americanin A [124], the coumarinolignans cleomiscosin A (**69**) and B [105], and lignans of Chinese lemon [110] also exhibit hepatoprotective properties. Hepatoprotective properties were also found in phenylpropanoids of roseroot rhizome [135].

Dicaffeoylquinic acids (DCQA) (**19**) isolated from Italian everlasting flowers are of great practical interest. They have been proposed as a new cholagogue preparation [33]. The cholagogic activity of artichoke DCQA, in particular, cynarin (**19**),

is known to be three times greater than that of monocaffeoylquinic acids (**18**) [37]. This indicates that DCQA may play an important role in the cholagogue activity of Italian everlasting.

Antimicrobial, analgetic, anti-inflammatory, and expectorant properties of phenylpropanoids must be mentioned. The antimicrobial and analgetic properties of eugenol (**26**) or clove oil produced from buttons of the clove tree [42] provide a classic example. Just as popular are expectorants based on essential oil of fennel (pharmaceutical dill) and common anise, the biological activity of which is due mainly to anethole (**27**) [40-42]. Reports indicating that fennel oil increases the antimicrobial activity of various plant extracts by 5-10 times are especially interesting. The pleasant smell of tarragon (tarkhun) is due to the main component of the essential oil, estragole (**25**), which provides the impetus for using this herb as a spice in various marinades and for producing the alcohol-free drink Tarkhun [155].

Flavonoids and hydroxycinnamic acids **7** and **8** are responsible for the antimicrobial and anti-inflammatory activities of preparations of propolis, extracts of poplar buds [8, 37]. Antimicrobial activity has been found relatively recently for other phenylpropanoids such as acteoside (**28**), forsythiaside (**29**), plantamajoside (**32**), forsythosides A, B, and C (**30**), and others [11, 73, 75, 79, 93, 141, 156-158]. Rosmarinic acid (**40**) and certain lignans have antiviral properties [10, 12, 144]. It should be mentioned that these research results explain the popularity in folk medicine of plantain leaves, which contain plantamajoside (**32**), as a wound-healing preparation. Plantain preparations are also used in folk medicine as an anti-ulcer agent. In our opinion, the use of plantain leaves as antimicrobial, anti-inflammatory, coating, and expectorant preparations in treating diseases of respiratory organs is justified. The antitviral and immunostimulating properties of medicinal plants such as medicinal melissa and purple echinacea, which contain rosmarinic (**40**) and cichoric (**24**) acids, respectively, also deserve attention [10, 12].

Research on the antimicrobial activity of phenylpropanoids isolated by us showed that caffeic acid (**7**) and several of its derivatives (**8**, **28**, **29**, and **40**) have the highest antibacterial activity toward *Staphylococcus aureus*. This agrees with the literature [37, 159]. The results indicate that the antimicrobial activity increases in the order ferulic acid (**8**) < rosmarinic acid (**40**) < caffeic acid (**4**) < forsythiaside (**29**) < acteoside (**28**). Using caffeic acid as an example, it was noted that substitution of the aromatic OH (**22**) and the carboxylic acid (**23**) can destroy the antimicrobial properties. A study of the structure—activity (antifungal) relationship revealed a slightly different order: *p*-coumaric acid > ferulic acid > caffeic acid. This emphasizes the need for further development of this area.

Neolignan isolated from *Zizyphus jujuba* leaves [144] and other phenylpropanoids [11, 55] can cause prostaglandin PGI_2, a valuable natural inhibitor of thrombocyte aggregation, to form on vascular walls. Analogous properties were described for phenylpropanoid glycosides of *Mussatia* species such as 4-cinnamoylmussatioside, 4-*p*-methoxycinnamoylmussatioside, and 4-dimethylcaffeoylmussatioside [100, 109]. The activity increases in this order.

Hypotensive activity has also been reported for feruloylamides [160], pinoresinol (*Eucommia ulmoides*) glucosides and diglucosides, and other phenylpropanoids [72, 161].

Roseroot, thorny eleutherococcus, common lilac, purple echinacea, medicinal melissa, and variegated milk-thistle deserve special attention.

6. MANUFACTURE AND STANDARDIZATION OF MEDICINAL PREPARATIONS BASED ON PLANT MATERIAL CONTAINING PHENYLPROPANOIDS

A voluminous amount of literature and the results of our research on medicinal plants containing phenylpropanoids indicate that effective medicinal preparations can be fabricated only based on a clear understanding of the chemical composition of the plant material, the identification of the BAC and accompanying compounds, their collective significance from the viewpoint of determining the authenticity, the quality of the medicinal starting material and preparations, and the determination of the pharmacological properties.

Therefore, we introduced the concept of pharmacognostic monitoring of plants [37], which enables objective process quality control during production and storage to be based on scientifically justified approaches to the standardization of medicinal plant material and preparations. Prerequisites for the development of new effective medicinal preparations can also be established.

In our opinion, the most important condition for the effectiveness of pharmacognostic monitoring is a systematic approach to the standardization of phytopreparations [162]. This consists of the unification (harmonization) of analytical methods in the order: raw material—substance—preparation. We also paid attention to the possibility of using the

corresponding State Standard Samples (SSS) in analytical methods for raw material and preparations in solving issues related to the fabrication and standardization of medicinal preparations based on plant material containing phenylpropanoids.

The advisability of using roseroot (rhizome and tissue-culture biomass), thorny eleutherococcus, medicinal melissa, variegated milk-thistle SSS rosavin (FS 42-0071-01), triandrin, syringin (VFS 42-2088-92), and rosmarinic acid and silybin (FS 42-0072-01) is based on research results [2, 27, 31-33, 102].

The quality of roseroot rhizome and liquid extract, which are used in medicinal practice as tonics and adaptogens, is evaluated using the salidroside content [132, 134], although we previously determined that salidroside occurs in most *Rhodiola* (L.) species and in significant quantities (~1%) in several of them [29, 32, 163, 165]. It was found that a diagnostic signature of roseroot rhizome is the presence of cinnamyl alcohol glycosides, which provides a basis for the thin-layer chromatography method used in the "Qualitative reaction" section of FS 75 (USSR State Pharmacopeia, XIth Ed.) for the determination of the authenticity of raw material from this plant. It was also found that the principal BAC of roseroot are, in addition to salidroside and tyrosol, cinnamylglycosides (rosavin, rosarin, rosin), the content of which in the raw material is ~4% [15, 30]. Therefore, we developed analytical methods for monitoring the content of rosavin and the total active components in roseroot raw material using SSS rosavin in the analysis [28, 37, 102, 166].

It is advisable to perform quality control of the raw material and preparations of this plant using rosavin content if the specificity of rosavin for roseroot rhizome, its biological activity, and the high content of the dominant cinnamylglycoside (up to 3.5%) in the raw material are considered [27, 29, 30-33, 166].

We improved further the analytical method for the roseroot raw material and preparations by studying the possibility of using the modern method of high-pressure liquid chromatography (HPLC) [28, 166].

Thus, studies of the chemical composition of roseroot rhizome, the principal results of which were the isolation of new BAC (phenylpropanoid glycosides) and the development based on this of an objective quality control method for the raw material, led to a re-examination of the drying conditions of the rhizome and yielded recommendations enabling the industrial cultivation and production of high-quality raw material to be performed rationally.

We formulated the concept of fabricating tonics based on phenylpropanoids using results of chemical and analytical research in addition to the chemical structure—biological activity relationships that were revealed. Plants containing cinnamyl-alcohol glycosides are most interesting as new medicinal stimulants and adaptogens. Considering that phenylpropanoid glycosides (cinnamylglycosides) exhibit greater stimulating activity than their aglycons, it is advisable to use approaches to standardization that would perform quality control of the raw material and preparations using the content of native cinnamylglycosides.

Having identified phenylpropanoids as the independent and principal group of BAC in roseroot rhizome [120, 162], the use in medical practice of liquid rhodiola extract, which contains a complex of active and accompanying compounds (phenylpropanoids, simple phenols, monoterpenes, flavonoids, tanning agents, etc.) that are responsible for the unique biological activity of this plant, seems justified. Research on the fabrication of new preparations based on roseroot rhizome must be performed with the intention of improving the technology of isolating the total substances and developing promising medicinal forms, for example, extracts and roseroot syrup in addition to medical patches, which have several advantages over traditional phytopreparations [167].

Research on expanding the indications for use of roseroot preparations as anticancer and anti-ischemic agents [147, 168] and on developing various combined preparations [169] is of current interest.

Biotechnology is one of the promising directions for guaranteeing a reliable raw-material supply for producing preparations [170-173]. The report [75] of the isolation of several phenylpropanoid glycosides, purpureasides A, B, and C, from leaves and callus tissue of purple digitalis deserves attention. Moreover, the phenylpropanoid content in this plant was not investigated.

Definite success has been achieved in the study of roseroot. Research on tissue- and cell-culture of this plant led as a first step to the development of a method for producing its biomass [71].

Pharmacologic investigations revealed distinct stimulating properties of aqueous-alcohol extracts of roseroot tissue-culture biomass [137, 138]. This indicates that it can be used advantageously in not only cosmetology but also medical practice.

We isolated several compounds belonging to the phenylpropanoid class during chemical studies of roseroot tissue-culture biomass [25, 57, 89]. These are derivatives of *p*-coumaryl alcohol (**2**) and *p*-coumaric (**6**) and caffeic (**7**) acids. It was found that two of the principal components of roseroot biomass are triandrin (*p*-coumaryl alcohol glucoside) (**14**) and lariciresinol glucoside (**43**). Therefore, the phenylpropanoid composition of roseroot biomass differs considerably from that of

the rhizome, consisting mainly of cinnamyl-alcohol (**1**) glycosides. The only analogy is that biosynthesis in roseroot biomass leads to the formation of triandrin, a hydroxylated rosin derivative that occurs in the rhizome. The fact that we did not detect salidroside and tyrosol in roseroot rhizome during our investigations [25] is remarkable. In our opinion, these were erroneously reported previously [174].

We proposed a spectrophotometric method for quantitative determination of phenylpropanoids to evaluate the quality of rhodiola tissue- and cell-culture biomass. Triandrin (**14**) and syringin (**17**) were used as standards [27].

The possibility of using HPLC for qualitative and quantitative analysis of roseroot biomass was also studied [25].

Rhizomes and roots of thorny eleutherococcus [*Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., Araliaceae] are sources of valuable tonics and adaptogens such as liquid and dried eleutherococcus extract [4, 18]. Data indicating that leaves and stem bark of this plant are also promising have appeared [59, 67]. Eleutherococcus preparations are also popular abroad, where this plant is sometimes called Siberian ginseng [19, 37, 69, 140]. The quality of rhizomes and liquid eleutherococcus extract is evaluated using the total content of eleutherosides B (syringin), B_1 (isofraxidin glucoside), and D (syringaresinol diglucoside) [175].

The use of SSS syringin was proposed in order to improve the analytical method for standardizing thorny eleuetherococcus raw material and preparations [33, 37, 102]. In particular, qualitative and quantitative HPLC analytical methods in addition to existing methods were introduced into FS 42-2725-90 (Revision No. 1) [176]. Foreign researchers [19, 69, 140] developed an HPLC method for monitoring the contents of eleutherosides B and D (separately).

It is noteworthy that qualitative analysis of thorny eleutherococcus raw material and preparations is also problematic. The problems are so serious that they do not preclude the possibility of counterfeit production. We proposed a thin-layer chromatography (TLC) method using SSS syringin for determining the authenticity of eleutherococcus raw material and preparations [37, 59].

We considered lilac bark as a possible medicinal raw material for preparing tonics and immunostimulating preparations as a result of research on the development of SSS syringin, the source of which was lilac bark, which contains 50 times as much of this compound as eleutherococcus [36].

Syringin (eleutheroside B) (**17**) is the principal phenylpropanoid glycoside of lilac bark (*Syringa vulgaris* L., Oleaceae) [36]. Other phenylpropanoids, flavonids, coumarins, iridoids, and derivatives of phenylethanol, including salidroside, were isolated from lilac bark during a chemical study [58, 91]. Among foreign studies, experiments on suspension culture of lilac leaf cells deserves special attention [172]. The total content of phenylpropanoids verbascoside and salidroside (phenylethanol glucoside), which is a biologically active component of roseroot, as noted above, reached 16% of the dry biomass.

A TLC method for determining the authenticity of this raw material, a chromatography-spectrophotometry method for quantitative determination of syringin, and an HPLC method for analyzing syringin were developed for standardization of lilac bark [36].

Neurotropic properties of lilac-bark extract showed that this substance increases the motor activity of mice by 40% compared with a control [136]. The immunostimulating properties of lilac bark are also very interesting because syringin is particularly active in this area and is the principal cinnamoylglycoside in this material [36, 136].

The genus *Echinacea* L., Asteraceae, includes five species of herbaceous perennials growing wild in North America [39, 44]. Among these, the most common are *Echinacea purpurea* (L.) Moench. = *Rudbeckia purpurea* L. and *Echinacea angustifolia* DC. var. *angustifolia*, which has been cultivated in Europe as a decorative plant since the 18th century [39]. The aerial part and roots of these plants are at present widely used in medical practice as immunomodulating, antimicrobial, and generally fortifying agents [39, 44]. Much valuable experience has been acquired in Germany, where a monograph on plants of the *Echinacea* L. genus was published [39]. Medicinal preparations such as Echinacin, Immunal, Echinaforce, Parodontax, and others, including combinations are sold in foreign countries. The raw material for the preparations is most often the herb and roots of purple echinacea [39]. Scientists of NPO "VILAR" proposed purple echinacea herb as medicinal plant material for preparing estifan, which consists of tablets of the dry extract (0.2 g) of this plant [44]. The preparation is recommended in medical practice as an immunostimulant for prophylaxis and treatment of immunodeficiency diseases [44]. Estifan is especially effective for inflammatory diseases of respiratory organs and stimulates the activity of cell and humoral units of the immune system, increases phagocytotic activity of neutrophils and macrphages, induces transformation of B-lymphocytes into plasmatic cells, and strengthens antibody formation, cooperation of B- and T-lymphocytes, and T-helper activity [44]. Furthermore, the echinacea preparation Galenofarm is sold in Russia and is in the final stage of state registration as an extract of purple echinacea. It was developed by scientists of the Samara State Medical University [34, 177-181].

According to domestic scientists, purple echinacea contains 2.3-5.0% total hydroxycinnamic acids [44]. Among these, cichoric acid (**24**) is the principal phenylpropanoid. It has been isolated by foreign investigators from most echinacea species [10, 39, 40].

According to German scientists [193], a second group of biologically active compounds that should be considered in addition to phenylpropanoids cichoric acid (**24**), echinacoside (**32**), etc., is the polysaccharides, which possess immunostimulating activity [150]. Polyacetylenated compounds with the isobutylamide moiety that were isolated from the herb and bark of purple echinacea are also interesting [39, 182].

A plant that combines immunomodulating and sedative properties is medicinal melissa (*Melissa officinalis* L., Lamiaceae) [12, 183]. It is widely used in folk medicine and is a pharmacopoeic plant in many countries [12]. The fact that about 300 preparations containing various substances from this plant (extracts, essential oil) are known in European countries gives an indication of the popularity of medicinal melissa [12]. Its leaves are used overseas as sedative, spasmolytic, analgesic, hypotensive, and digestion-improving agents [12]. The wide spectrum of therapeutic activity of medicinal-melissa preparations is due to the presence of BAC of various classes. Essential oil, the content of which in the raw material is 0.02-0.2% and in some instances up to 0.8%, is considered to be responsible for the sedative and spasmolytic activities [12]. About 190 components of the essential oil have been described. The principal ones are citral, citronellal, linalool, geraniol, nerol, caryophyllen, etc. [12, 60]. Citronellal has the greatest sedative effect; geraniol and citronellol, spasmolytic properties [12].

Phenylpropanoids represent another group of BAC (rosmarinic, caffeic, chlorogenic, and other hydroxycinnamic acids) that are responsible for immunomodulating, antiviral, anticancer, and antimicrobial properties of extracts of this plant [12]. Medicinal melissa was known mainly as an oil-bearing plant and has only comparatively recently begun to be used in official medicine [4, 183], including foreign combination preparations (Novo-Passit, nervoflux, persen, etc.).

An evaluation by TLC of the chemical composition of the phenolic compounds in medicinal melissa grown in Moscow and Samara districts, Crimea, and Krasnodar territory showed that rosmarinic acid (**73**) is the dominant component in all instances [60]. Further investigation of medicinal melissa isolated rosmarinic acid, its ethyl ester, flavonoids of cynaroside, cosmosiin, and luteolin, and daucosterol [60].

The quality of medicinal melissa is evaluated overseas using the essential-oil content [at least 0.05% according to the German pharmacopoeia (DAB 10)] [12, 129]. A TLC method for essential-oil components, in particular, citral, is used to determine the authenticity of the raw material [12]. The wide distribution of citral among many oil-bearing plants of the Labiatae family prompted us to study the possibility of identifying medicinal melissa material using a different group of compounds.

In our opinion, the presence of not only essential-oil components but also rosmarinic acid, which is the characteristically dominant phenylpropanoid, should be determined to monitor the authenticity and quality of medicinal melissa raw material. This approach to standardization is even more acute for determining the authenticity of new medicinal preparations developed by us (extracts and syrup of melissa), where the detection of essential-oil components is problematic, especially with the low content of essential oil in the raw material.

Our research showed that it is advisable to evaluate the raw material (FS 42-3645-98 medicinal melissa herb) and medicinal melissa preparations using the phenylpropanoid content [184].

Variegated milk-thistle [*Silybum marianum* (L.) Gaertn., Asteraceae] occupies a special place among phenylpropanoid plants. Its fruit is used widely abroad to produce valuable hepatoprotective preparations such as karsil, legalon, silybor, etc. [3-5, 7, 37]. The most significant domestic preparations are sibektan, silymar, etc. [185-187]. However, as before, the expensive foreign preparations dominate the RF pharmaceutical market [3, 42, 189].

The potential for manufacturing domestic hepatoprotective preparations based on flavolignans from fruit of variegated milk-thistle is great in Samara district. The most expansive industrial source of raw material from this plant was established at the collective farm "Sergievskii" even during Soviet times. Fruit of variegated milk-thistle is used to treat various liver diseases in its powdered form and to prepare a thick oil with wound-healing and hepatoprotective properties [190]. Milk-thistle oil is used to prepare an extract of medicinal plants (erksol), which has been proposed as an anti-inflammatory, wound-healing, and anti-ulcer agent [185]. We developed the new hepatoprotective medicinal agent liquid milk-thistle extract [178, 191-198]. It is important to mention that fruit and defatted raw material (waste from oil production) of variegated milk-thistle are intended for use in preparing it. This solves the problem of complete use of raw material from this plant. Furthermore, its extract is included in the new medicinal preparation silybochol [199], in line with the current tendency to formulate combination preparations based on milk-thistle fruit [37, 177].

A process for complete recycling of variegated milk-thistle raw material was developed using the research results. Medicinal forms such as powdered native and defatted fruit, milk-thistle oil and extract (VFS 42-3381-99), and the combination preparations silybochol, silydon, and rastospir can be produced [28, 146, 178, 180, 195-205].

Keeping in mind that the biological activity of preparations from variegated milk-thistle fruit is due to flavolignans which, analogously to other natural lignoids, possess immunomodulating activity [3, 37, 58, 82, 165], we investigated the immunotropic properties [205] and found that the mechanism of action of the milk-thistle extract is similar to that of the known immunomodulator purple echinacea [3, 58]. The research results indicate that liquid milk-thistle extract is promising for use as not only a hepatoprotector but also an immunomodulating agent, especially for treating patients with professional damage to the liver and other organs of the gastrointestinal system with a weakened humoral immunity and phagocytosis.

TLC analysis that increases the objectivity in evaluating raw-material quality was proposed for determining the authenticity of variegated milk-thistle fruit (VFS 42-3180-99) and liquid milk-thistle extract (VFS 42-3181-99) [37, 204]. The dominant BAC silybin, silydianin, and silychristin can be clearly separated. Illumination of the chromatograms in UV light (254 nm) detects the compounds as bright violet fluorescent spots with R_f values of 0.8 (at the level of SSS silybin), 0.7, and 0.6, respectively.

In principle, it is important that we propose using silybin as a standard (FS 42-0072-01) to standardize fruit and hepatoprotective preparations of variegated milk-thistle, including in the “Qualitative reactions” section.

In our opinion, HPLC is a promising method for qualitative analysis of raw material and variegated milk-thistle preparations in view of the variability of the chemical composition [37, 131]. This method can combine qualitative and quantitative determination of the flavolignans [204, 206].

Therefore, the drive to fabricate new medicinal preparations based on variegated milk-thistle fruit and to improve the analytical methods is, as before, strong because they can both broaden the variety of effective hepato- and ecoprotectors and also rationally use the existing raw-material supply.

Information on the hepatoprotective activity of flavolignans from fruit of variegated milk-thistle in combination with the anti-oxidant and immunomodulating properties will help to use this medicinal plant as a promising source of raw material to prepare new highly effective hepatoprotective preparations that have a holistic protective action on the human organism.

Thus, phenylpropanoids, which occur in many medicinal plants, are very interesting for fabricating effective tonic, immunostimulating, anticancer, hepatoprotective, antimicrobial, and anti-inflammatory phytopreparations. This provided a basis to recognize phenylpropanoids as an independent group of BAC and was reflected in the chemical classification of medicinal plants [13, 82, 121].

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