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Symphytum Species: Distribution, Biochemistry, Pharmacology, Ecology, and Research Perspectives

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This review covers the most important aspects of research on plants of the genus *Symphytum* L. (Boraginaceae Juss.), such as distribution, morphological features, use, biochemical characteristics, ecological, pharmacological, and phytoremediation features. Plants from the genus *Symphytum* have been used in folk medicine since ancient times. *Symphytum officinale* L. (comfrey), as the most studied species from this genus, has been used from ancient times for treating pain, inflammation, and swelling in muscles and joints, particularly in conditions like degenerative arthritis, acute back pain, sports injuries, ulcers, wounds, bone fractures, and rheumatic complaints. This knowledge stimulated new investigations, which included more species from this genus, that represented in pharmacological, biological, and ecological reviews. Important pharmacological properties of these plants include anti-inflammatory, anti-ulcer, antioxidant, antimicrobial, and regenerative effects. In general, it should be noted that the results available in scientific sources on the study of this species mainly concern *S. officinale*, while other species have been studied fragmentarily or there is no information at all. Future research could and should focus on a more in-depth and broader systematic analysis of the genus, microbiological aspects of the study (use of more species and strains of microorganisms), ecological aspects (lack of data on allelopathic activity and salt tolerance), and the bioremediation potential of other species besides *S. officinale*.

Keywords: comfrey, biochemical composition, pharmacological properties

Introduction

Since ancient times, humans have discovered the benefits of the plant world and begun to use plants for food, medicinal purposes, and survival (Petrovska Bauer, 2012; Šantić et al., 2017; Hardy, 2018). Today, innovative approaches to the study of plant raw materials have achieved incredible results in various fields of modern biology and medicine, such as molecular biology, biotechnology, genetics, phytomedicine, pharmacology, ecology, physiology, and plant biochemistry (Wasiullah et al., 2025). On the one hand, plant biodiversity needs to be controlled for various reasons, especially in the context of global change (Furey and Tilman, 2021; Obiar et al., 2024). However, nowadays, phytodiversity offers both

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forgotten and new plant species for widespread use, or plant material that requires more in-depth research in connection with the rapid development of humanity and technology (Ahluwalia et al., 2024). In this case, the search for new plant species with a wide range of uses and beneficial properties remains an important task in solving specific problems in the economic sector and agriculture.

Recent studies have focused on many herbaceous plants, both annuals and perennials, that are of scientific interest for the purpose of creating new scientifically based products, but some of them, such as representatives of Boraginaceae Juss., are controversial (Stanojeva et al., 2023). Species of one of the oldest genera of Mediterranean origin, namely *Symphytum* L., are of scientific interest not only in pharmacological studies of plant raw materials, but also in the study of the ecological behaviour of plants in plant communities, in the study of many systematic issues, etc.

Known since antiquity for its medicinal, nutritional, and agricultural uses, *Symphytum* includes species with high biomass productivity, diverse phytochemical profiles, and notable pharmacological and ecological properties (Salehi et al., 2019). However, despite long-standing interest, most available data concern *S. officinale* L., while other species remain poorly investigated or are known only fragmentarily.

Therefore, a comprehensive and updated analysis of *Symphytum* species is needed to consolidate existing knowledge, identify research gaps, and outline future directions for biological, ecological, and applied studies of this genus.

Distribution

Symphytum (comfrey) is an Eurasian genus that belongs to Boraginaceae Juss. family with approximately 40 species, with the distribution center in the Pontic area in the western part of the Irano-Turanian region. The distribution range is Europe, Asia Minor, and Southwestern Asia (Kobrlová, 2022). Five additional non-native species originating mostly from eastern Europe, the eastern Mediterranean, and the Caucasus are also reported: *S. asperum* Lepech., *S. bulbosum* K. F. Schimp., *S. caucasicum* M. Bieb., *S. orientale* L., and *S. tauricum* Willd. *S. bohemicum* F.W. Schmidt, *S. officinale* L., *S. tanaicense* Steven (*S. officinale* complex), and *S. cordatum* Waldst. are native species to Central Europe (Kobrlová et al., 2016). Carpatian subendemic *S. cordatum* needs protection in Lviv Oblast of Ukraine, which would contribute to the preservation of regional biodiversity and the gene pool of this species (Kobiv, 2023), and it is a rare species in the North of Slovakia (Orava region) (Hrivnák et al., 2024). Mosyakin and Fedoronchuk (1999) reported about ten species of the *Symphytum* genus in the Ukrainian Flora.

In addition to the recognized species, the genus includes several natural and cultivated hybrids, such as *S.* × *uplandicum* (*S. asperum* × *S. officinale*), *S.* × *norvince* (*S. asperum* × *S. orientale*), and

Figure 1 Inflorescences of *Symphytum asperum* Lepech. and *S. caucasicum* M. Bieb. with buds and flowers in the M.M. Gryshko Botanical Garden of the National Academy of Sciences of Ukraine

Figure 2 Inflorescences of *Symphytum* × *uplandicum* Nyman. and *S.* × *mosquense* S.R. Majorov & D.D. Sokoloff with buds and flowers in the M.M. Gryshko Botanical Garden of the National Academy of Sciences of Ukraine

S. caucasicum × *S. orientale*, which further contribute to the morphological and biochemical variability of the group (Leaney, 2019; Salehi et al., 2019).

Some Central European and regionally rare *Symphytum* species require conservation, and the presence of natural and cultivated hybrids enhances the genus's biodiversity and genetic resource potential.

Morphological, Phenological, and Reproductive Characteristics

These are perennial species with stems are branched, hollow, and strongly winged, with ridges running down the internodes from the leaf bases; all plants (besides *S. tanaicense* stems) are covered in long, downward-pointing, bristly hairs, which are softer on the leaves; leaves alternate along the stem, oval-lanceolate, long-lanceolate, elliptic and upper leaves have margins that extend down the stem. The colour of leaves ranges from light green (*S. tanaicense*), green (*S. asperum*), dark green (*S. officinale*, *S.* × *uplandicum*), and sometimes green-grey (*S. caucasicum*). The colour of the corolla is light blue (*S. caucasicum*), bright blue (*S. asperum*) (Figure 1), violet (*S. officinale*) (Figure 3), rose-cream (*S.* × *uplandicum*) (Figure 2), and white (*S. orientale*, *S. tauricum*) (Figure 4). The shoot number per plant was 5.15–10.05, depending on species, which grow in the Ukrainian conditions (Vergun, 2006a). The anomaly flowers and stems (fasciation) of *S. asperum* and *S. caucasicum* plants (Vergun, 2006b; Vergun, 2008a) were fixed.

Plants are characterized by self-pollination (Hou et al., 2021) or by insects (Goulson et al., 1998). The main pollinators of *Symphytum* spp. are *Bombus* spp. The mass of pollen per 100 anthers is 9.87 mg (Denisow, 2008).

Flowering onset occurred in the following species order: *S. caucasicum* >*S. bohemicum* >*S. officinale*, *S. tanaicence* >*S. asperum*. The inflorescences are cymose, with the average value per plant being 40.27 (*S. asperum*), 10.90 (*S. caucasicum*), 5.93 (*S. bohemicum*), 5.53 (*S. officinale*), and 4.73 (*S. tanaicence*). Flowers are white, blue, violet, rose colours with amounts of 70.1 (*S. asperum*), 58.42 (*S. bohemicum*), 109.25 (*S. caucasicum*), 76.25 (*S. officinale*), and 41.03 (*S. tanaicence*) pieces per plant (Vergun, 2008a).The fruits are nutlets (Kong and Hong, 2016) with four erems, which differ in the genus range by the surface structure and ornamentation (Vergun, 2007; Akçin and Baki, 2009). The Turkish species is characterised by tuberculate and rugose types of fruit surface structure (Akçin and Baki, 2009).

They are used as a forage plant (Uteush and Lobas, 1996; Denisow, 2008), for energetic purposes (for biomethane production) (Ţîtei et al., 2024). The addition of *S. officinale* extracts with symbiotics or separately to the broiler and turkey diets increased feed intake intensity and is an alternative to antibiotics (Oliveira et al., 2016; Pandey et al., 2023). Despite the numerous studies about pyrrolizidine alkaloid content, the comfrey leaves have been successfully

Figure 3 *Symphytum officinale* L. in the Slovak Republic (Nitransky region, Ludanice village)

tested as a dietary supplement for pigs.The positive effect on microbiota was observed (Oster et al., 2021). Also, the use of biochar pyrolyzed (higher than 550 °C) from *S. officinale* is recommended as ecologically acceptable (Du et al., 2019). *Symphytum* spp. are fast-growing species that can be harvested 4–5 times a year (Salehi et al., 2019).

Symphytum species are perennial, fast-growing plants with diverse leaf and flower morphology, insect- or self-pollinated reproduction, and high flowering and fruiting variability; their rapid growth and adaptability make them valuable for forage, biomethane production, and dietary supplementation.

Biochemical characteristics

The main substances in various extracts of *Symphytum* spp. were different groups of polyphenols, including flavonoids and phenolic acids (Table 1). These components usually determine the antioxidant properties of plant raw materials (Lang et al., 2024). The qualitative composition of phenolic acids at the species level is presented below in the description of each specific species.

Figure 4 Inflorescences of *Symphytum tairicum* Willd. with buds and flowers in the M.M. Gryshko Botanical Garden of the National Academy of Sciences of Ukraine

Table 1 Antioxidant compounds in *Symphytum* spp. extracts

Species	Component	Extract	Content	Reference
***S. aintabicum*, above-ground part**	TPC	methanol	91.80 mg GAE·g^{-1}	Zengin et al., 2021
	TPC	water	72.31 mg GAE·g^{-1}	
	TFC	methanol	25.12 mg RE·g^{-1}	
	TFC	water	8.90 mg RE·g^{-1}	
***S. anatolicum*, whole plant**	Rutin	methanol	8.58 mg·g^{-1} (of extract)	Kilinc et al., 2023
	Rosmarinic acid	methanol	3.18 mg·g^{-1} (of extract)	
	3,4-dihydroxyhydrocinnamic acid	methanol	1.65 mg·g^{-1} (of extract)	
***S. officinale*, leaves**	TPC	methanol	8.44 mg GAE·g^{-1}	Lou et al., 2023
	TFC	methanol	66.98 mg QE·g^{-1}	
***S. officinale*, roots**	TPC	water	0.72 mg GAE·g^{-1}	Stefanov et al., 2025
	TFC	water	64.84 mg QE·g^{-1}	
***S. officinale*, roots**	TPC	ethanol	29.79 mg GAE·g^{-1}	Chociej et al., 2024

Notes: TPC – total polyphenol content, TFC – total flavonoid content, GAE – gallic acid equivalent, RE – rutin equivalent, QE – quercetin equivalent

Available sources on various species of this genus indicate a diverse quantitative and qualitative content of compounds of various nature, such as allantoin, organic acids, alkaloids, mono- and polysaccharides, which make them pharmacologically valuable plant raw materials.

The comprehensive biochemical study of *S. anatolicum* (whole plant) showed the presence of the following compounds: allantoin, 2,5-dihydroxybenzoic acid, 4-hydroxybenzoic acid, caffeic acid, benzoic acid, rutin, quercetin-3-O-glucoside, saponarin, kaempferol 3-O-glucoside, kaempferol 3-O-galactoside, 3,5-O-DCQA, ferulic acid, *rosmarinic* acid, salvianolic acid A, salvianolic acid B, salvianolic acid C, and monomethyl lithospermate. Sugars (sucrose, fucose, maltotriose) and organic acids (pyrrolidonecarboxylic acid, succinic acid, 4-Hydroxybenzoic acid, malonic acid, glutaric acid, fumaric acid, malic acid) were also determined (Kilinc et al., 2023). Another study, concerning the water root extracts, also demonstrated the presence of saccharides and polysaccharides (fructans, inulin) and monosaccharides (sucrose, fructose, and glucose) (Stefanov et al., 2025).

S. officinale extract investigations showed a wide range of variability in chemical composition (total phenolic compounds, alkaloids, phenolic acids) in the plant obtained from different regions of Europe (Trifan et al., 2021; Trifan et al., 2025).

The main components of *S. asperum*, *S. caucasicum*, and *S. grandiflorum* extracts were phenolic acids, flavonoids, and pyrrolizidine alkaloids (PAs), according to the study of Luca et al. (2024). PAs are secondary plant metabolites, with hepatotoxic and cancerogenic properties characterized by antimicrobial, anti-inflammatory, antivirus, and antitumor activities (Wei et al., 2021). The following PAs of *Symphytum* species roots are known: symphytine, echimidine (Furuya and Hikichi, 1971), symviridine (Roeder et al., 1992), 3-Acetyllycopsamine, 7-Acetyllycopsamine, heliosupine, etc. (Onduso et al., 2017). Echimidine-*N*-oxide (three diastereoisomers), 7-sarracinyl-9-viridiflorylretronecine (two diastereoisomers), echimidine (two diastereoisomers), lycopsamine (two diastereoisomers), dihydroechinatine-*N*-oxide, dihydroheliospathuline-*N*-oxide, lycopsamine-*N*-oxide (three diastereoisomers), 7-acetyllycopsamine-*N*-oxide, symphytine-*N*-oxide (two diastereoisomers), and 2″,3″-epoxyechiumine-*N*-oxide were determined in root extracts of *S. cordatum* Waldst. ex Kit. (Mroczek et al., 2006).

However, research is being conducted on *S. officinale* and *S.* × *uplandicum* to reduce the PA content by breeding (Ruzicka et al., 2021).

These species are a rich source of allantoin that plays an important role in plant stress tolerance and use in the cosmetic industry (Kaur et al., 2023). The content of allantoin in *S. officinale* roots was 15.14–36.46 mg·g^{-1} DW (Hawrylak-Nowak and Dresler, 2023). Also, the allantoin content was higher in the root aqueous extract obtained by enzymatic ultrasonic extraction than by ultrasonic extraction only (Dinica et al., 2021).

The free amino acid content in leaves of *Symphytum* spp. collected in Ukraine was from 13.90 (*S. asperum*) to 427.07 (*S. tanaicence*) mg·g^{-1}. Leaves of

S. bohemicum predominated in threonine content, serine, and phenylalanine; histidine was predominant in *S. officinale* leaves and *S. tanaicence* in glutamic acid (Vergun, 2008b).Hontova (2009; 2013) investigated that *S. caucasicum* herb contains proline, aspartic acid, glutamic acid, methionine, arginine, while the *S. officinale* herb had the most tyrosine, methionine, glutamic acid. Both roots contained the most methionine, but *S. caucasicum* roots were rich in phenylalanine and arginine, and *S. officinale* roots in arginine and tyrosine also. The Turkish endemic *S. anatolicum* is characterised by the presence of N-methyl-aspartic acid, tyrosine, valine, isoleucine, and alanine (Kilinc et al., 2023).

Symphytum species contain diverse bioactive compounds that determine their medicinal, cosmetic, and nutritional potential, with some species being selectively bred to reduce toxic metabolites.

Pharmacological Properties

Plants of the *Symphytum* genus, especially *S. officinale*, are widely recognized as pharmacologically valuable raw materials. Plants of this genus from ancient times are recommended for external and internal uses due to a wide spectrum of essential properties (Salehi et al., 2019). S. offcinale has been used for treating pain, inflammation, and swelling in muscles and joints, particularly in conditions like degenerative arthritis, acute back pain, sports injuries, ulcers, wounds, bone fractures, and rheumatic complaints (Staiger, 2012; Trifan et al., 2025). This species is also used in ethnoveterinary medicine for the healing effect on injured skin in cows (Mahdy et al., 2019).

The investigations of antioxidant activity of the different species from the *Symphytum* genus showed that the aerial part of the plants is most active compared with roots (Luca et al., 2024). *S. caucasicum*, among other Caucasian medicinal plants, exhibited significant antioxidant activity (Rivello et al., 2024). Methanol and ethanol *S. caucasicum* extracts obtained in the spring vegetation demonstrated high free radical scavenging activity (FRSA), while the water extracts had maximal values of FRSA in the flowering stage (Vergun et al., 2017). According to Zengin et al. (2021), the extracts of *S. aintabicum* exhibited high antioxidant activity: 0.56–232.34 mg $TE \cdot g^{-1}$ by DPPH method, 10.9.98–389.96 mg $TE \cdot g^{-1}$ by ABTS method, 106.20–575.69 mg $TE \cdot g^{-1}$ by CUPRAC method, 47.89–379.90 mg $TE \cdot g^{-1}$ by FRAP method, 0.82–2.79 mM $TE \cdot g^{-1}$ by phosphomolybdenum method, and metal chelating ability was 16.77–19.64 mg $EDTA \cdot g^{-1}$. Antioxidant activity of leaf extracts was also determined for *S. officinale* (Lou et al., 2023).

The anti-inflammatory potential of *Symphytum* spp. is attributed to a range of bioactive compounds, including allantoin (*S. anatolicum*, *S. caucasicum*, *S. officinale*, *S.* × *uplandicum*), *rosmarinic* acid (*S. anatolicum*, *S. asperum*, *S. cordatum*, *S. officinale*), hydro caffeic acid (*S. cordatum*, *S. officinale*), *rosmarinic* acid (*S. anatolicum*, *S. asperum*, *S. cordatum*, *S. officinale*), etc. (Mahmoudzadeh et al., 2022). However, investigations on the molecular level concerning the anti-inflammatory activity require a deep study (Seigner et al., 2019).

Along with antioxidant, anti-inflammatory properties, the *S. officinale* extracts exhibited a protective effect on liver tissues (Majeed, 2023) and antinociceptive activity (Vostinaru et al., 2018). The comprehensive study of creams based on *S. officinale* extracts on rats demonstrated the regenerative properties of the skin (Mârza et al., 2024). The antibacterial properties of natural polyethers were determined in *S. asperum*, *S. caucasicum*, and *S. grandiflorum* extracts (Merlani et al., 2022).

Recent studies recommend *S. officinale* root extracts with optimized levels of allantoin and *rosmarinic* acid for cosmetic applications (Dresler et al., 2023). Furthermore, leaf extracts of this species have been successfully used in the synthesis of silver nanoparticles with skin-photoprotective properties(Singh et al., 2018).

International Nomenclature of Cosmetic Ingredients recommended *S. officinale* root extracts as antiseborrhoeic, skin-conditioning, leaf powder as abrasive, and leaf extracts as skin conditioning components (Chrzanowska et al., 2024; Melnyk et al., 2024). Leaf extracts of *S. officinale* demonstrated the antiulcer effect (Bakr et al., 2024).

Symphytum species possess significant pharmacological potential, including antioxidant, anti-inflammatory, hepatoprotective, antibacterial, and regenerative effects, making them valuable for medicinal and cosmetic applications.

Ecological and Phytoremediation Features

Plants of the *Symphytum* genus are mesophytes that typically grow in forests, such as in the Carpathian region (*S. cordatum* Waldst. et Kit. ex Willd.) (Kobiv, 2023), as well as in mountainous areas of the Black Sea and Mediterranean regions (Hacioğlu and Erik, 2013), often near rivers. Studies of Turkish *Symphytum* species indicate that *S. aintabicum* and *S. bornmuelleri* prefer clayey-loam, low-salinity soils with a pH of 7.08–7.98 (Yakupoğlu et al., 2020). *S. officinale* has been recommended as drought-adapted, demonstrating resilience under water-limited conditions (Silva et al., 2023).

In addition to their ecological adaptability, *Symphytum* species exhibit significant phytoremediation potential. Soil contamination by heavy metals is a global environmental concern, and *S. officinale* has been shown to chelate Pb ions *in vitro* through root tannins (Chin et al., 2009).

Further studies demonstrated that *S. officinale* can accumulate Cd, Zn, and Pb, contributing to soil recultivation.The species' high tolerance to heavy metal stress may be regulated by the expression of key genes, making it a suitable model for studies on multi-metal resistance improvement(Xu et al., 2024).

Interactions with soil microorganisms further enhance phytoremediation efficiency. Experiments using *Streptomyces pactum* and *Bacillus consortia* showed increased Zn and Cd concentrations in roots compared to shoots, altering metal bioavailability and translocation(Ali et al., 2021). Conversely, exposure to heavy metals negatively affected morphometric parameters, biomass, chlorophyll synthesis, and antioxidant status under both single and combined stress conditions(Sun et al., 2025). The study of the rhizosphere of cultivated *S. officinale* on contaminated soils (Cd/Zn) showed changes in rhizosphere microorganism structure (*Proteobacteria* and *Ascomycota*) and a decrease in heavy metal content. The increase in microorganism abundance in soil activated defense mechanisms under heavy metals (Guo et al., 2024).

Symphytum species are ecologically versatile, thriving in forests, mountains, and riverine areas, with some drought tolerance. They also demonstrate significant phytoremediation potential, particularly *S. officinale*, which can accumulate and detoxify heavy metals, with efficiency enhanced by interactions with soil microorganisms.

Conclusions

Symphytum spp. are multipurpose plants and a valuable source of biologically active compounds, plant raw material for forage and energetic purposes, and potential phytoremediants. In general, it should be noted that the results available in scientific sources on the study of this species mainly concern *S. officinale*, while other species (*S. aintabicum*, *S. anatolicum*, *S. asperum*, *S. caucasicum*, *S. cordatum*, etc.) have been studied fragmentarily or there is no information at all. On the other hand, there are issues regarding information on productivity, ecological growth, some important systematic issues, and allelopathic activity. All these issues may help to find a wider range of uses for these plant species in agriculture, cosmetics, and the pharmaceutical industry. Over the past decades, important data have been obtained on the biochemical components of the above-ground and underground parts of various plant species, their potential use as fodder, and as promising plants capable of withstanding drought and the effects of heavy metals. In general, studies focused on one or a group of species from a single region, whereas a more detailed comparative analysis of different species would allow for an assessment of biological characteristics, introduction potential, ecological status of plants, and biochemical evaluation of plant raw materials for use in various sectors of the national economy and the preservation of biodiversity in different parts of the globe. Future research could and should focus on a more in-depth and broader systematic analysis of the genus, microbiological aspects of the study (use of more species and strains of microorganisms), ecological aspects (lack of data on allelopathic activity and salt tolerance), and the bioremediation potential of other species besides *S. officinale*. The search for new environmentally friendly technologies requires an innovative approach to finding new sources of plant raw materials, so plants of the *Symphytum* genus deserve more in-depth research, as existing data indicate the high competitive ability of certain species of this genus.

Conflicts of Interest

The authors have no competing interests to declare.

Ethical Statement

This article does not include any studies that would require an ethical statement.

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