International Scientific Conference
UNITECH`2024

PHYTOCHEMICAL CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF COMFREY (*SYMPHYLUS OFFICINALE* L.).

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Abstract

Comfrey (Symphylus officinale L.) has a long history of use as a medicinal plant. Modern randomized controlled trials have confirmed the effectiveness and safety of comfrey preparations for treating pain, inflammation, and swelling in muscles and joints, particularly in conditions like degenerative arthritis, acute back pain, and sports injuries, including sprains, contusions, and strains. Other researchers hypothesized that comfrey is a valuable source of biologically active compounds, particularly dietary fiber with potential prebiotic properties, because it contains polysaccharide inulin and fructooligosaccharides. The purpose of this paper is to providing evidence about Comfrey's biological activity, antioxidant potential, and phytochemical profile. Also to evaluate its role and application in both the food and pharmaceutical industries.

Keywords: comfrey, medicinal, plant, biologically, active, compounds, polysaccharide, inulin, fructooligosaccharides.

INTRODUCTION

Comfrey (*Symphylus officinale* L.), a plant with a long history of medicinal use, has been traditionally employed for healing wounds, treating respiratory and gastrointestinal issues, and reducing inflammation. It contains various compounds, including allantoin, triterpenes, tannins, and phenolic acids, which contribute to its therapeutic properties [1].

Comfrey root contains beneficial compounds such as polysaccharides, phenolic acids, and vitamins. These substances contribute to its anti-inflammatory and moisturizing effects.

Comfrey also contains pyrrolizidine alkaloids, which are toxic and can cause liver damage. This toxicity has led to restrictions on the use of comfrey in many countries [1]. Therefore, it's crucial to use comfrey products responsibly and under medical supervision [2].

Recent research has been focusing on identifying the beneficial compounds in comfrey that are not associated with toxicity. This study aimed to analyze the phenolic compounds in a comfrey root extract using advanced analytical techniques. The results revealed the presence of various phenolic compounds, including rosmarinic acid and salvianolic acids, which are known for their antioxidant and anti-inflammatory properties [2].

Further research is needed to fully understand the therapeutic potential of comfrey root extract and to develop safe and effective formulations for medicinal use.

EXPOSITION

In addition to the comfrey root, the above-ground parts of the plant (*Symphyti herba*) and its leaves (*Symphyti folium*) are also used for medicinal purposes. Different clinical trials have been conducted on ointments containing extracts from these plant parts, showing their effectiveness in treating conditions such as wound healing, muscle pain, and acute ankle sprains [1,2].

Wound Healing with a topical ointment containing 10% active ingredients from the aerial parts of comfrey (*Symphytum*

doi: www.doi.org/10.70456/IEMH9021

uplandicum) has been evaluated for wound-healing effects in a randomized, double-blind clinical trial involving 278 patients with fresh abrasions. The study showed a faster reduction in wound size of 49 ± 19% per day in the comfrey group compared to 29 ± 13% in the reference group ($p<5\times10^{-21}$). Complete healing occurred 2.97 days faster with comfrey, and efficacy was rated as good to very good by 93.4% of physicians, compared to 61.7% for the reference product ($p=2\times10^{-11}$). No adverse effects or drug tolerance issues were noted [2].

Treatment for muscle pain (*Myalgia*) with the same comfrey-based topical ointment was tested for myalgia relief in a double-blind, randomized trial with 215 patients experiencing such pain [3]. Pain reduction in the treatment group was significantly greater than in the referenced group for pain during movement, at rest, and on palpation, with an efficacy rating of good to excellent. Onset of relief was also faster with the high-concentration ointment, which was well-tolerated [3].

A study of 203 patients confirmes the efficacy of a comfrey ointment with 10% active ingredient for pain relief and functional improvement in acute ankle sprains. Symptom scores for pain and swelling improved significantly by days 3 and 4. A comparison with a low-dose reference product also showed meaningful results, highlighting the use of comparator products in herbal trials when placebo use is challenging [3].

An open study with 105 patients suffering from musculoskeletal pain found that twice-daily application of the comfrey cream fully resolved symptoms in 57 patients, with partial or moderate improvement in most others. Comfrey proved most effective for muscle pain, swelling, and overstrain, though less so for pain associated with osteoporosis.

In a 5-day randomized, double-blind trial with 120 patients, a comfrey root extract cream reduced acute upper or lower back pain by approximately 95.2% compared to 37.8% in the placebo group, indicating rapid relief within 1 hour of application. Adverse effects were mild and infrequent, with the study suggesting a fast-acting effect on pain reduction [4].

A comfrey cream was also assessed in a trial with 220 patients with knee osteoarthritis, showing significant reductions in pain, stiffness, and functional impairment compared to placebo. Quality of life and mobility improved, with no adverse effects noted in the active therapy group. The study emphasized the difficulty of placebo creation in herbal studies and noted successful blinding measures in this trial [4].

Despite its diverse functions, the role of allantoin, found in comfrey, has a part in regulating many biological processes related to cell proliferation remains insufficiently explored [4]. In the 1990s, it is introduced the concept of “protective catabolism,” based on the idea that degradation products of intracellular biopolymers, particularly DNA, have various non-specific protective functions. Later, the protective effect of allantoin was experimentally confirmed [4]. The first mention of allantoin dates back to 1838, when it was shown that uric acid can be oxidized to allantoin. Subsequent studies revealed the presence of allantoin and uric acid in the urine of dogs and other animals, and by 1909, allantoin was recognized as an endogenous metabolite in dogs, cats, rabbits, and monkeys.

Small quantities of allantoin were detected in human urine and in amniotic fluid. However, at that time, the scientific community was convinced that uric acid could not be oxidized in the human body [4]. The "rehabilitation" of allantoin occurred in the early 1990s when studies on oxidative stress rediscovered allantoin as a product of uric acid oxidation. Research showed allantoin to be a more sensitive marker of oxidative stress than glutathione and cysteine. [4]

Previous studies demonstrates that, under conditions of oxidative stress induced by hyperbaric oxygenation, allantoin modulates the activity of the enzymatic antioxidant system, increasing levels of intracellular H_2O_2, which serves as a secondary messenger for certain growth factors, activating tyrosine kinase activity in many proteins and stimulating proliferation. At the same time, allantoin mitigates H_2O_2-induced mutagenesis and reduces the toxic effects of high H_2O_2 concentrations. [5]

Increased allantoin synthesis has also been observed in the human body following intense physical activity, likely due to the activation of free radical oxidation. This phenomenon could also be interpreted as a regeneration process of muscle cells, involving the formation of non-specific metabolic factors that stimulate cell proliferation and growth. We believe allantoin is one of these factors, supported by its effect on the membrane transport of ureidosuccinate, an intermediate in the pyrimidine biosynthesis pathway. [5]

Assuming that certain metabolic pathways lost during human evolution may still be present in embryonic tissues, we examined allantoin content in the developing human placenta and in the serum of pregnant women.

The carbohydrate composition, shown in table 1, with 95% ethanol and subsequent aqueous extracts of comfrey root has been analyzed. Additionally, individual sugars and inulin content have been determined using HPLC-RID [6].

Results from the different analyses indicated that inulin (fig. 1) is the primary storage carbohydrate in comfrey roots [6]. Previous studies by Van Laere and Van Den Ende only mentioned *Symphytum officinale* L. as a source of inulin. Other reserchers reports the presence of glucofructan in the roots of *Symphytum officinale* L., with low molecular weight at the beginning of the vegetation period and high molecular weight at the end. In their study, low molecular weight fructans were detected at 11%, while high molecular weight fructans were found at 29.5%. This results for the high molecular weight fructan fraction (27.6 g/100 g) closely align with other findings, while the low molecular weight fraction (in the ethanol extract) is more than three times lower. This discrepancy could be explaned with the differences in harvest and climate conditions. Moreover, the total fructan content shows higher results in the subsequent water extract (27 g/100 g), which is consistent with previously reported values of 15-30% [6].

Table 1: CARBOHYDRATES CONTENT IN EXTRACTS OF COMFREY ROOTS, G/100 G DW (MEAN ± SD, N=3) [6]

Carbohydrates	**Comfrey Extracts**		
	95% Ethanol	***Water***	***Total***
Uronic acid content	0.3±0.1	1.7±0.2	2.0±0.2
Total fructans	4.9±0.5	27.6±1.0	32.5±0.5
Inulin	0.3± 0.1	24.9± 2.2	25.2± 2.2
Nystose	0.1± 0.0	-	0.1± 0.0
1-Kestose	0.3± 0.1	-	0.3± 0.1
Sucrose	1.8± 0.5	1.5± 0.5	3.3± 0.5
Glucose	2.3± 0.5	-	2.3± 0.5
Fructose	5.1±0.2	1.0± 0.4	6.1± 0.3

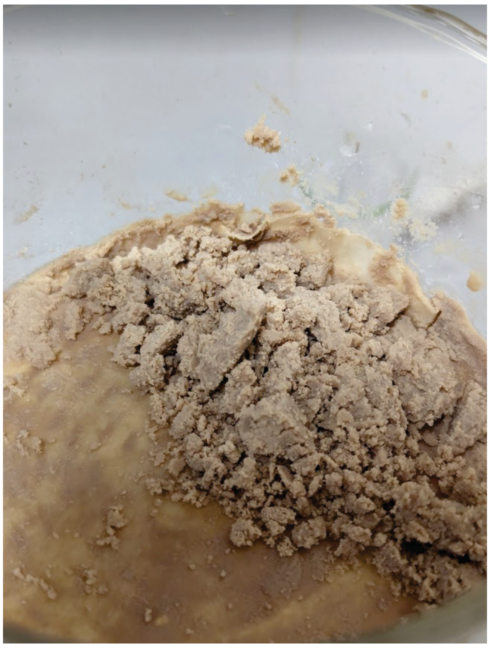

Figure 1. Extracted inulin from *Symphylus officinale L.*

Inulin (IN) is a plant-derived fructan polysaccharide composed of varying numbers of fructose units linked by β-(2→1)-D-fructosyl-fructose bonds, typically ending with a D-glucopyranosyl residue connected via an α-(1→2) bond. Originally isolated in 1804 from Inula helenium, inulin is widely found as a storage carbohydrate in over 30,000 plant species, including chicory and Jerusalem artichoke. Certain bacteria and fungi also produce inulin [5]. Due to its high inulin content, chicory and Jerusalem artichoke are now primary sources for industrial inulin production. Research over recent decades has highlighted inulin's value as a natural, compatible nutrient with various bioactivities, including blood sugar and lipid regulation, anticancer properties, microbiota support, and enhanced mineral and vitamin absorption. Recognized as a natural food ingredient in the EU, inulin is increasingly applied across food and pharmaceutical sectors. This paper reviews recent advances in inulin's physiological benefits and its potential pharmaceutical applications [5].

Physicochemical Properties

In its dry form, inulin appears as an amorphous, odorless powder with a spherical crystal structure and molecular weight between 5600–6300 g/mol. Inulin can lower water's freezing point or raise its boiling point, is non-reducing, and shows left-handed optical activity in water. A hydrophilic compound, inulin is only slightly soluble in cold water or ethanol but highly soluble in hot water, with solubility increasing with temperature. For instance, natural inulin's solubility rises from 6% at 10°C to 33% at 90°C. Polymerized long-chain inulin, like that from ORAFTI, has minimal solubility at lower temperatures, though solubility significantly increases at higher temperatures. Inulin's crystalline structure greatly influences its solubility; four crystalline polymorphs (α, β, γ, and δ) exhibit unique thermodynamic stability and solubility profiles, with updated research identifying additional polymorphs and amorphous forms. [5]

Stability

Inulin exhibits strong thermal stability, with minimal degradation at temperatures up to 100°C. However, it is hydrolyzed into fructose and glucose under acidic conditions ($pH < 4$), which limits its use in highly acidic beverages. Inulin gels are quite stable, as the lack of free water reduces hydrolysis risk. The four crystalline polymorphs also differ in thermodynamic stability, ordered from least to most stable as $\beta < \alpha < \gamma < \delta$.

Prebiotic Effect

Prebiotics are indigestible dietary components that enhance host health by promoting the growth and activity of beneficial bacteria. As a well-known prebiotic, inulin (IN) supports digestive health, immune function, and nutrient absorption by resisting digestion in the upper gastrointestinal tract and undergoing fermentation in the colon. This fermentation process helps relieve constipation, which is especially beneficial for older adults, and can increase stool moisture and improve intestinal health. Additionally, IN promotes beneficial gut bacteria like Bifidobacteria, making it a potential treatment for conditions like inflammatory bowel disease (IBD). Studies have shown that inulin fermentation produces short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which serve as energy sources and support cell health, further benefiting gut function. Furthermore, factors like degree of polymerization (DP) and storage conditions can influence IN's effectiveness as a prebiotic, with shorter-chain inulins exhibiting higher prebiotic activity[5].

Antioxidant Effect

While oxidation is essential for energy production, it can lead to cellular damage from free radicals, contributing to diseases like cancer and aging. Antioxidants counteract these effects by reducing free radicals. Inulin exhibits antioxidant properties, enhancing the activities of enzymes that protect cells from oxidative stress. Additionally, SCFAs produced from inulin fermentation support antioxidant activity. Studies indicate that inulin with a lower DP has higher antioxidant potential. Research in animal models has confirmed inulin's ability to boost antioxidant enzyme levels and reduce markers of oxidative stress. Structural modifications to inulin, like grafting with amino groups or catechins, have yielded derivatives with even greater antioxidant capabilities, highlighting inulin's potential role in health and aging treatments [5].

CONCLUSION

In summary, the above-ground parts and root of comfrey (*Symphytum officinale* L.) have demonstrated significant therapeutic benefits across various clinical applications. Studies confirm that comfrey-based creams and ointments are effective for wound healing, muscle pain, joint sprains, back pain, and osteoarthritis. Clinical trials show these treatments consistently outperform low-dose reference products or placebos, providing faster pain relief, reducing swelling, and improving functional mobility without adverse effects. This suggests that comfrey extracts offer a reliable, well-tolerated option for topical treatment of musculoskeletal and soft tissue injuries. The research supports further consideration of comfrey as a natural, fast-acting alternative for pain management and healing.

The study of allantoin reveals its largely underexplored role in regulating biological processes, especially cell proliferation. Initially identified as an oxidation product of uric acid, allantoin has been observed to increase in response to oxidative stress and physical activity, suggesting it as a sensitive marker of oxidative stress. Beyond its antioxidant properties, allantoin appears to promote cellular growth by modulating enzyme activity and supporting tissue repair and regeneration. This is particularly evident in muscle recovery post-exercise and during embryonic development, where allantoin may play a role in stimulating growth and managing oxidative damage. These findings highlight allantoin's potential as a protective and regenerative agent in cellular processes, warranting further research into its therapeutic applications.

Inulin, a plant-derived polysaccharide, is widely used in food and pharmaceuticals due to its biocompatibility, health benefits, and ease of availability. It has multiple physiological functions, including blood sugar and lipid regulation, anticancer effects, and support for gut health. Inulin's physical properties, like solubility and stability, vary with temperature, molecular structure, and crystallinity. Highly stable thermally, inulin can degrade in acidic conditions, limiting its use in certain products. Overall, inulin's versatile applications and beneficial properties make it a valuable natural ingredient in various industries.

Inulin acts as both a prebiotic and antioxidant, offering multiple health benefits. As a prebiotic, inulin supports digestive health by fostering beneficial gut bacteria, enhancing nutrient absorption, and alleviating constipation, particularly in older adults. It can also aid in managing conditions like inflammatory bowel disease (IBD) by producing short-chain fatty acids (SCFAs) that nourish gut cells. Additionally, inulin has antioxidant properties that combat free radicals, reducing oxidative stress and associated aging effects. Modifications to inulin's structure have increased its antioxidant potential, further highlighting its therapeutic potential in promoting gut and overall cellular health.

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