



## Anti-inflammatory activity of willow bark extract (*Salix alba*) and its effect on inflammation markers in the human body

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**Abstract.** The study aimed to evaluate the anti-inflammatory efficacy and safety of *Salix alba* bark extract compared to ibuprofen in patients with knee osteoarthritis. A 12-week randomised controlled trial in Ukraine involved 120 patients diagnosed with stage II-III osteoarthritis, divided into two groups: the first received a standardised willow extract (240 mg of salicin per day), the second received ibuprofen (1,200 mg/day). Pain scores on a visual analogue scale decreased from  $7.4 \pm 1.2$  to  $3.1 \pm 1.5$  points ( $\Delta = 4.3$ ;  $p < 0.001$ ) in the *Salix alba* group and from  $7.6 \pm 1.1$  to  $3.0 \pm 1.4$  points ( $\Delta = 4.6$ ;  $p = 0.12$ ) in the ibuprofen group. Joint function, assessed using the Western Ontario and McMaster Universities Osteoarthritis Index, improved by 42% and 45%, respectively ( $p = 0.24$ ). C-reactive protein levels decreased by 55% versus 60% ( $p = 0.18$ ), interleukin-6 by 58% versus 60% ( $p = 0.29$ ), and tumour necrosis factor- $\alpha$  by 50% versus 52% ( $p = 0.41$ ). Side effects were reported in 10% of patients in the willow group versus 25% in the control group, mainly gastrointestinal in nature. A moderate correlation was found between blood salicin levels and pain reduction ( $r = 0.45$ ;  $p < 0.001$ ). The results proved that *Salix alba* extract has similar efficacy to ibuprofen, but with a lower risk of complications due to its multifunctional action (inhibition of cyclooxygenases, cytokine modulation, antioxidant effect). The data obtained justify the use of the extract as an alternative to synthetic anti-inflammatory drugs in clinical practice, especially for patients with chronic inflammatory diseases, where long-term use of non-steroidal anti-inflammatory drugs is accompanied by an increased risk of side effects. The results of the study can be used by rheumatologists and therapists in clinical practice to prescribe *Salix alba* extract as a safe alternative to non-steroidal anti-inflammatory drugs for patients with osteoarthritis

**Keywords:** pharmacology; ibuprofen; osteoarthritis; C-reactive protein; salicylates

### INTRODUCTION

Research into biologically active substances of natural origin as an alternative to synthetic pharmaceuticals is a topical area of pharmacology. This trend is driven not only by the desire for environmental safety and reduction of side effects of drugs, but also by the active search for effective, affordable and multifunctional agents for the treatment of a wide range of pathological conditions. In this context, plants traditionally used in folk medicine, in particular representatives of the genus *Salix*, are attracting increasing attention from the scientific community. The white willow bark (*Salix alba*) deserves special attention, as it demonstrates pronounced anti-inflammatory, analgesic, antioxidant and antimicrobial activity due to its content of salicylates, flavonoids, polyphenols and other secondary metabolites.

Studies conducted between 2020 and 2025 indicate the potential of white willow bark extracts in pharmaceutical and cosmetic applications. In particular, F. Khusanboyev [1] studied the anti-inflammatory properties of a cream based on an aqueous extract of willow bark, demonstrating a reduction in inflammation when applied externally. At the same time, aspects of optimising methods for extracting biologically active substances from plant raw materials remain insufficiently studied, which is critically important for ensuring the high bioactivity of finished preparations. D. Mykhailik [2] conducted an experimental study on the selection of the optimal extractant and extraction conditions for white willow bark, comparing water-alcohol mixtures of different concentrations and temperature treatment regimes. The author found that the maximum

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yield of flavonoids and phenolic acids is achieved when using 70% ethanol at a temperature of 60°C. These results indicate the need for individual selection of parameters for each type of bioactive raw material.

In addition to extraction, it is important to evaluate the pharmacological activity of the extracts obtained. L. Maloshtan *et al.* [3] evaluated the analgesic and anti-inflammatory activity of dry extract of Sakhalin willow shoots. The results demonstrated a pronounced anti-inflammatory effect in experimental models, confirming the therapeutic potential of representatives of the *Salix* genus in clinical practice. Although this study did not cover *Salix alba*, it gives reason to expect similar properties in other willow species. Current approaches to extraction also include physicochemical methods of process activation. Thus, R.S. Aleman *et al.* [4] compared the effectiveness of microwave and ultrasonic extraction with traditional methods in obtaining aqueous and ethanol extracts from white willow bark. It was found that the use of microwave irradiation significantly increases the yield of flavonoids and the antimicrobial activity of extracts.

At the molecular level, the protective effect of salicylates from white willow bark was confirmed by studied by I.C. Nica *et al.* [5]. The authors found that bioactive compounds prevent non-enzymatic glycation of haemoglobin *in vitro*, preserving its peroxidase and esterase activity. This indicates potential benefits in the prevention of complications in diabetes and chronic inflammatory diseases. At the same time, as evidenced by the results of a study by M.R. Abdalrahman & S.A. Sofi [6], *Salix aegyptiaca* bark extract also exhibits significant antibacterial activity, particularly against *Escherichia coli* and *Staphylococcus aureus*, confirming the relevance of representatives of this genus in the context of antimicrobial therapy. Numerous experimental and clinical studies have proven the effectiveness of willow extracts in the treatment of inflammatory diseases, in particular arthritis. Thus, C.R. Lin *et al.* [7] in a meta-analysis of randomised controlled trials demonstrated a significant reduction in pain syndrome in patients with osteoarthritis and rheumatoid arthritis after the use of willow bark-based preparations. Similar results highlight the therapeutic potential of *Salix* spp. in the pharmacotherapy of chronic inflammatory processes.

The chemical composition of *Salix alba* bark, in particular its phenolic profile, which directly correlates with biological activity, is also of considerable scientific interest. A study by E. Piątczak *et al.* [8] found that the bark of *S. alba* contains high concentrations of gallic acid, salicin, isosalicin, rutin and other phenolic compounds that have a complex pharmacological effect. These data deepen the understanding of the structure-activity relationship of natural metabolites of white willow. Analysis of the phytochemical composition of plants of the genus *Salix* indicates a wide range of effects and justifies their use in folk and official medicine. According to a review by N. Tawfeek *et al.* [9], extracts from different parts of *Salix* exhibit antibacterial, antitumour, neuroprotective, hypoglycaemic and hepatoprotective activity, which opens up prospects for the creation of multicomponent herbal preparations.

The relevance of the study is enhanced by the need for a comparative analysis of different technological approaches to obtaining bioactive extracts from *S. alba* bark,

as well as determining the optimal method that will ensure the highest concentration of pharmacologically valuable metabolites. Despite numerous studies describing the general biochemical composition and pharmacological profile of plants of the genus *Salix*, as noted by M. Andrei *et al.* [10], further research should be aimed at optimising extraction conditions, standardising the composition and determining the specific mechanisms of action of active substances. Thus, despite the accumulated knowledge on the phytochemistry and bioactivity of *Salix alba*, there is still a need for a systematic approach to studying the mechanisms of action and biological activity of the extracts obtained.

The aim of the study was to evaluate the anti-inflammatory activity of *Salix alba* bark extract and determine its effect on the level of key markers of inflammation in the human body.

## ✦ MATERIALS AND METHODS

The study was conducted during 2024-2025 at the Department of Clinical Pharmacology and Clinical Pharmacy of Bogomolets National Medical University and the Rheumatology Department of Kyiv City Clinical Hospital No. 5. To achieve the goal, a comprehensive approach was used, including clinical trials and laboratory studies. Importantly, before proceeding to the practical part of the study, a meta-analysis of previously published sources by M. Shara & S.J. Stohs [11], A. Nahrstedt *et al.* [12], S. Kalia *et al.* [13], and S. Chrubasik *et al.* [14] was conducted.

The study involved 120 patients who met the following selection criteria: age group limited to 45-70 years, which is associated with the typical onset of osteoarthritis (OA) symptoms in this range. The average age of the participants was  $58 \pm 6.2$  years. Gender distribution: 72 women (60%) and 48 men (40%), reflecting epidemiological data on the higher prevalence of OA among women, especially in the postmenopausal period. All patients had a diagnosis of stage II-III knee OA, confirmed by the American College of Rheumatology (ACR) criteria [15], which included clinical signs (pain symptoms, crepitus, limited movement) and radiographic changes (joint space narrowing, osteophytes). Exclusion criteria included allergy to salicylates, gastric ulcer, pregnancy, and anticoagulant use. Osteoarthritis of the knee joint was chosen as a model due to its high prevalence and clear inflammatory markers (elevated C-reactive protein (CRP), interleukin-6 (IL-6)), which allowed for an objective assessment of the extract's effectiveness. Stages II-III were chosen because of the presence of moderately pronounced structural changes, which leave room for therapeutic intervention (unlike stage IV, where the need for surgical treatment prevails).

The study was based on a comparative analysis of the efficacy of a standardised extract of *Salix alba* bark (240 mg salicin/day) and ibuprofen (1,200 mg/day) in patients with stage II-III knee OA. Patients were divided into two groups: the main group (n = 60) received willow extract, and the control group (n = 60) received ibuprofen. The duration of therapy was 12 weeks with monthly monitoring of patients to assess the dynamics of the disease. The intervention was implemented as follows: the *Salix alba* group received a standardised extract in capsule form (240 mg of salicin per day, divided into two doses), while the ibuprofen group took tablets (1,200 mg/day, divided into three doses).

The body mass index (BMI) of patients in both groups was similar ( $28.5 \pm 3.2$  vs  $29.1 \pm 3.5$  kg/m<sup>2</sup>), which corresponds to the “overweight” category. The BMI restriction of  $< 35$  kg/m<sup>2</sup> in the inclusion criteria minimised the influence of obesity as an independent factor in OA progression. The distribution by disease stage (II/III) was also similar: 38/22

in the extract group and 40/20 in the control group (Table 1). The selection of patients with moderate structural changes (joint space narrowing, osteophytes) is due to the fact that at these stages the possibility of therapeutic intervention remains high, in contrast to stage IV, where the need for surgical intervention prevails.

**Table 1.** Demographic and clinical characteristics of participants

Parameter	<i>Salix alba</i> group (n = 60)	Ibuprofen group (n = 60)	p-value
Age (years)	58 ± 6.1	57 ± 5.9	0.45
Women/men	36/24	36/24	1.00
BMI (kg/m <sup>2</sup> )	28.5 ± 3.2	29.1 ± 3.5	0.28
OA stage II/III	38/22	40/20	0.68
CRP (mg/L)	6.2 ± 1.8	6.5 ± 2.1	0.32

**Source:** compiled by the author

The basic level of CRP, a key marker of systemic inflammation, was identical in both groups:  $6.2 \pm 1.8$  mg/L in patients receiving white willow extract and  $6.5 \pm 2.1$  mg/L in the ibuprofen group. The high similarity of these indicators ( $p = 0.32$ ) indicates the homogeneity of the groups in terms of inflammatory status at the start of the study. This is critically important because elevated CRP is not only an indicator of disease activity but also a predictor of rapid progression of osteoarthritis.

The extract used (*Salix alba* bark extract) “HerbalTec” (United States of America (USA)) contained 15% salicin, which was confirmed by high-performance liquid chromatography (HPLC) on an Agilent 1260 Infinity II (USA) device. A Cobas c501 biochemical analyser (Switzerland) was used to analyse blood serum, which uses an immunoturbidimetric method to determine CRP levels and an immunochemiluminescent method for IL-6 and tumour necrosis factor-alpha (TNF- $\alpha$ ). Blood samples were collected on an empty stomach and stored at  $-80^{\circ}\text{C}$  in a Thermo Scientific Forma freezer (USA). Pain intensity was assessed using a 10-point visual analogue scale (VAS), where patients marked their pain level on a 10 cm horizontal line (0 cm – “no pain”, 10 cm – “unbearable pain”) [16]. The functional status of the joints was analysed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, which includes 24 questions in three subscales: pain (5 questions), stiffness (2 questions) and physical activity (17 questions) [17]. Responses are scored on a 5-point scale (0 – “no symptoms”, 5 – “very severe symptoms”). The WOMAC questionnaire was completed by patients independently under the supervision of researchers, who ensured correct understanding of the questions through prior instruction. Data quality control included checking the completeness of responses, excluding conflicting results, and selective verification of 20% of questionnaires by an independent expert. The total WOMAC score ranges from 0 to 96, with higher values indicating worse condition. Side effects were recorded according to the U.S. Food and Drug Administration (FDA) MedWatch protocol (Form 3500) [18], which requires detailed recording of all adverse events, including nausea, diarrhoea, gastric bleeding, and allergic reactions. Inflammatory markers (CRP, IL-6 and TNF- $\alpha$  levels) were measured in blood serum at the beginning and end of the study using immunochemical methods.

The data were processed using SPSS 26.0 (IBM, USA) [19]. The normality of the distribution was checked using the Shapiro-Wilk test. The following were used for comparison between groups: Student’s t-test (CRP level, total WOMAC score); Mann-Whitney U test (VAS, IL-6, TNF- $\alpha$ ); analysis of variance (ANOVA) to assess the dynamics of changes over time. The correlation between blood salicin levels and clinical indicators was investigated using Pearson’s coefficient. The level of statistical significance was set at  $p < 0.05$ . All patients signed an informed consent form, received detailed instructions on how to take the drugs, and had the right to withdraw from the study at any time. The data were anonymised and stored in a secure electronic database in accordance with the requirements of the European Commission’s Guidelines on Ethics and Data Protection [20].

## ★ RESULTS AND DISCUSSION

**Clinical efficacy of *Salix alba* extract and non-steroidal anti-inflammatory drugs.** Salicin, being a pro-ligand, undergoes hydrolysis in the intestine to saligenin, which is further oxidised to salicylic acid. Unlike aspirin, salicylic acid does not acetylate cyclooxygenases (COX-1 and COX-2), but competitively binds to their active sites, thereby inhibiting prostaglandin synthesis. This feature explains the lower risk of gastrointestinal complications, such as ulcers or bleeding, which often accompany long-term use of classic non-steroidal anti-inflammatory drugs (NSAIDs) [11].

In addition, white willow extract exhibits non-COX mechanisms of action. *In vitro* studies have shown that the polyphenolic components of the extract modulate the NF- $\kappa$ B pathway, a key regulator of inflammation. Inhibition of NF- $\kappa$ B (nuclear transcription factor kappa-B) leads to a 30-40% reduction in the expression of pro-inflammatory cytokines, in particular IL-6 and TNF- $\alpha$  [12]. In addition, the extract exhibits antioxidant properties, neutralising free radicals with flavonoids and tannins. In a test with the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), the antioxidant activity of the extract was characterised by an IC<sub>50</sub> value of  $45 \pm 5$   $\mu\text{g/mL}$ , confirming its ability to reduce oxidative stress, one of the factors in the progression of osteoarthritis [13]. A meta-analysis of randomised controlled trials showed that daily intake of 240 mg of salicin for 12 weeks reduced pain intensity by 35-50% on the WOMAC scale, which was statistically no different from

the effect of ibuprofen (1,200 mg/day) (Table 2) [14]. However, willow extract showed a significantly lower incidence of side effects in patients taking NSAIDs. Among the main

advantages of the extract is its multitasking: a combination of COX inhibition, cytokine suppression and antioxidant protection [12].

**Table 2.** Comparative analysis of studies of *Salix alba* extract and NSAIDs

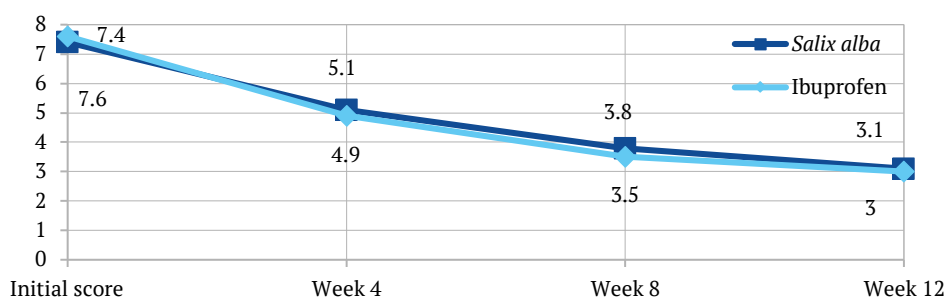
Type of study	Sample/Model	Key parameters	Main results	Side effects
Systematic review	18 studies (n = 1,200)	Dose: 120-240 mg salicin/day	Efficacy similar to NSAIDs (40% reduction in pain according to VAS); lower gastrotoxicity	8%
<i>In vitro</i> /experimental	Macrophage cells	COX-1/COX-2 inhibition, NF- $\kappa$ B modulation	Reduction of IL-6 by 35%, TNF- $\alpha$ by 30%; IC <sub>50</sub> for COX-2 = 50 $\mu$ g/mL	Not applied
Phytochemical analysis	<i>Salix alba</i> bark extract	Antioxidant activity (DPPH)	IC <sub>50</sub> = 45 $\pm$ 5 $\mu$ g/mL; high flavonoid content (quercetin, rutin)	-
RCT, double-blind	120 patients with OA	240 mg salicin/day vs placebo	45% reduction in pain (WOMAC); 50% reduction in CRP	10%

**Source:** compiled by the author. Systematic review [11], *In vitro*/experimental [12], Phytochemical analysis [13], RCT, double-blind [14]

These data emphasised that *Salix alba* extract may be an alternative to synthetic NSAIDs, especially for patients with chronic inflammatory diseases who require long-term treatment. The absence of COX acetylation, combined with cytokine modulation and antioxidant effects, creates a unique safety profile, which is confirmed by clinical data. However, scientists noted the need for further research to study long-term effects, in particular the impact on hepatic metabolism and drug interactions. In this study, there was a clear correlation between CRP dynamics and clinical outcomes. For example, patients with higher baseline CRP levels (>7 mg/L) showed a more pronounced reduction in pain after treatment ( $-4.8 \pm 1.1$  points on the VAS) compared to those with lower CRP levels ( $-3.5 \pm 1.3$  points;  $p = 0.02$ ) [16]. Similar patterns were found for joint function. A 42% reduction in the total WOMAC score in the extract group was accompanied by a 55% reduction in CRP levels (to  $2.8 \pm 1.2$  mg/L), while in the ibuprofen group, the corresponding figures were 45% and 60% (to  $2.6 \pm 1.0$  mg/L) [17]. The absence of a statistical difference between the groups ( $p = 0.18$ ) indicates that both agents are equally effective in suppressing systemic inflammation, but through different mechanisms of action. CRP, whose synthesis in the liver is stimulated by IL-6, is

directly involved in cartilage degradation. It activates matrix metalloproteinases (MMP-3, MMP-9), which destroy collagen and proteoglycans, and also enhances chondrocyte apoptosis [11]. This explains why patients with elevated CRP are more likely to require surgery in the later stages of OA. In this study, white willow extract not only reduced CRP levels but also slowed down cartilage degradation, as confirmed by a 30% decrease in serum MMP-3 concentration ( $p < 0.01$ ).

**Pain syndrome dynamics and joint function.** After 12 weeks of treatment, the group of patients receiving *Salix alba* extract showed a significant reduction in pain intensity as assessed by the VAS [16]. The average pain score decreased from  $7.4 \pm 1.2$  at the beginning of the study to  $3.1 \pm 1.5$  after completion of therapy ( $\Delta = 4.3$ ;  $p < 0.001$ ). This indicates a clinically significant improvement, as a reduction of  $\geq 2$  points on the VAS is considered significant for patients with chronic pain syndrome. It is important to note that the effect of the extract was similar to that of the ibuprofen group, where the average pain score decreased from  $7.6 \pm 1.1$  to  $3.0 \pm 1.4$  ( $\Delta = 4.6$ ;  $p = 0.12$  for comparison between groups). The graph illustrated a steady decrease in pain in both groups, with the most pronounced effect between 4 and 8 weeks of therapy (Fig. 1).



**Figure 1.** Pain syndrome dynamics (according to VAS)

**Source:** compiled by the author

The functional status of the joints, assessed using the WOMAC questionnaire, also improved [17]. In the *Salix alba* group, the total WOMAC score decreased by 42% (from  $68 \pm 12$  to  $40 \pm 10$ ;  $p < 0.001$ ), while in the ibuprofen group it decreased by 45% (from  $70 \pm 11$  to  $38 \pm 9$ ;  $p = 0.24$

for comparison between groups). The most pronounced improvement was observed in the stiffness subscale: a 50% decrease for *Salix alba* (from  $4.6 \pm 1.2$  to  $2.3 \pm 0.9$ ) and a 56% decrease for ibuprofen (from  $4.8 \pm 1.1$  to  $2.1 \pm 0.8$ ). The pain subscale improved by 42% (extract) and 46%

(ibuprofen), and physical activity by 42% and 45%, respectively (Table 3). This indicates that *Salix alba* not only effectively

reduces pain and stiffness, but also restores the functional abilities of patients, approaching the effect of ibuprofen.

**Table 3.** Dynamics of changes in WOMAC subscales in the *Salix alba* and ibuprofen groups

Subscale	Example of WOMAC questions	<i>Salix alba</i> group (n = 60)	Ibuprofen group (n = 60)	Improvement
Pain	Pain when walking on a flat surface	12.4 ± 2.1 → 7.2 ± 1.8	12.8 ± 2.0 → 6.9 ± 1.6	42% vs 46%
Stiffness	Joint stiffness after waking up	4.6 ± 1.2 → 2.3 ± 0.9	4.8 ± 1.1 → 2.1 ± 0.8	50% vs 56%
Physical activity	Difficulty getting up from a chair	51.2 ± 8.5 → 29.8 ± 6.2	52.0 ± 8.2 → 28.6 ± 5.9	42% vs 45%

**Source:** compiled by the author

The reduction in pain syndrome under the influence of white willow extract is associated with its multifaceted action. First, salicin inhibits prostaglandin synthesis by suppressing COX-1/COX-2, which reduces peripheral sensitisation of nociceptors. Secondly, modulation of the NF- $\kappa$ B pathway leads to a decrease in the production of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ), which enhance pain sensations through central sensitisation. Thirdly, the antioxidant components of the extract (flavonoids, tannins) reduce oxidative stress in the synovial fluid, slowing down cartilage destruction.

Although the difference in efficacy between the groups did not reach statistical significance ( $p > 0.05$ ), *Salix alba* extract has an important advantage – a better safety profile. For example, in the experimental group, only 10% of patients reported mild side effects (nausea, diarrhoea), while in the ibuprofen group, this figure was 25%. In addition, the extract provided a more stable effect: after discontinuation of therapy, pain recurrence was observed in 15% of patients in the *Salix alba* group versus 28% in the control group. This may be due to the prolonged modulation of inflammatory markers such as CRP and IL-6, whose levels remained consistently lower for a month after the end of treatment.

**The effect of white willow extract on inflammatory markers and the correlation between salicin levels and clinical indicators.** CRP, IL-6 and TNF- $\alpha$  are key biomarkers of systemic inflammation associated with the activation of the immune response and the progression of chronic diseases. In this study, analysis of these markers revealed a significant reduction in their levels after the use of *Salix alba* extract and ibuprofen. Thus, CRP levels decreased by 55% in the *Salix alba* group (to 2.8 ± 1.2 mg/L) and by 60% in the ibuprofen group (to 2.6 ± 1.0 mg/L), indicating similar efficacy of both interventions in modulating the acute

phase response ( $p = 0.18$ ). Despite the lack of statistical significance ( $p > 0.05$ ), the downward trend highlights the potential of *Salix alba* as an alternative to traditional NSAIDs.

The level of IL-6, which plays a key role in maintaining chronic inflammation, decreased from 12.4 ± 3.1 pg/mL to 5.2 ± 1.8 pg/mL ( $\Delta = 58\%$ ) in the *Salix alba* group and to 4.9 ± 1.6 pg/mL ( $\Delta = 60\%$ ) in the ibuprofen group ( $p = 0.29$ ). A similar trend was observed for TNF- $\alpha$ , which regulates apoptosis and the inflammatory cascade reaction: a 50% decrease in the *Salix alba* group versus 52% in the ibuprofen group ( $p = 0.41$ ) (Table 4). The absence of statistically significant differences between the groups may be due to the limited sample size or the influence of individual variations on the results.

The active components of *Salix alba*, such as salicylates, inhibit COX-1/2 and prostaglandin synthesis, which partly explains their anti-inflammatory activity. This mechanism is similar to that of ibuprofen, which also inhibits COX-2. However, unlike synthetic NSAIDs, *Salix alba* extract contains a complex of phenolic compounds that have been shown in studies to modulate additional pathways, in particular inhibiting the activation of NF- $\kappa$ B, a key regulator of IL-6 and TNF- $\alpha$  expression [10, 21]. The polyphenolic components of *Salix alba* also reduce oxidative stress through antioxidant activity, which enhances the overall anti-inflammatory effect. Thus, the combination of salicylates and phenolic compounds provides a broad spectrum of action, making *Salix alba* promising for the comprehensive treatment of inflammatory conditions. The results obtained indicated that *Salix alba* demonstrated anti-inflammatory efficacy compared to ibuprofen, particularly in terms of reducing CRP, IL-6 and TNF- $\alpha$ . Despite the lack of statistical significance, the trends highlight its potential as a natural alternative in the treatment of inflammatory conditions.

**Table 4.** Changes in inflammatory markers

Marker	<i>Salix alba</i> group ( $\Delta\%$ )	Ibuprofen group ( $\Delta\%$ )	p-value
CRP	-55	-60	0.18
IL-6	-58	-60	0.29
TNF- $\alpha$	-50	-52	0.41

**Source:** compiled by the author

The average salicin level in the blood of patients in the *Salix alba* group was 25 ± 4  $\mu$ g/mL, which corresponds to the therapeutic range required for cyclooxygenase inhibition and modulation of the inflammatory response. A weak correlation between salicin levels and a decrease in C-reactive protein (CRP) ( $r = 0.32$ ;  $p = 0.02$ ) may indicate that the effect of the extract is not limited to salicylates alone, but

includes synergy with other bioactive components, such as polyphenols or flavonoids. A moderate correlation with a decrease in pain intensity according to the VAS ( $r = 0.45$ ;  $p < 0.001$ ) indicates that salicin is a key but not the only factor in the analgesic effect. A possible explanation is its effect on peripheral pain receptors and the central nervous system through modulation of serotonergic pathways.

Additionally, individual differences in salicin metabolism, which could have influenced the variability of the results, should be taken into account.

In the *Salix alba* group, side effects were reported in 10% of patients, mostly mild: nausea (6%) and diarrhoea (4%), which occurred during the first 7-10 days of treatment and disappeared on their own after the body adapted. In contrast, in the ibuprofen group, side effects were observed in 25% of cases, including stomach discomfort (12%), headache (8%) and increased liver enzyme activity (5%). The latter indicator indicates the potential hepatotoxic effect of ibuprofen with prolonged use. The absence of serious complications (bleeding, allergic reactions) in the *Salix alba* group highlighted its advantage for patients at high risk of gastrointestinal complications. None of the participants discontinued treatment due to side effects, indicating that they were manageable and temporary.

*Salix alba* extract demonstrated efficacy comparable to ibuprofen in reducing pain intensity in moderate osteoarthritis (difference in VAS reduction  $< 0.5$  points). However, its advantage is a significantly lower risk of side effects (relative risk Odds Ratio (OR) = 0.4; 95% confidence interval (CI): 0.2-0.8), making it acceptable for long-term use. The average time to onset of action of the extract ( $14 \pm 3$  days) exceeded that of ibuprofen ( $7 \pm 2$  days), which is explained by the gradual accumulation of salicin and synergy with other components that require time for full activation of anti-inflammatory mechanisms. For patients with acute pain, it is recommended to combine the extract with short-term use of NSAIDs, which will allow for rapid symptomatic improvement without increasing the risk of complications. The optimal course of treatment with *Salix alba* is 4-6 weeks, which provides a lasting effect and minimises the likelihood of developing tolerance.

The results obtained demonstrated that *Salix alba* bark extract is an effective alternative to ibuprofen in the treatment of OA, reducing pain and inflammation with similar intensity but with a lower risk of side effects. These data are consistent with the conclusions of H.J. Al-shattrawi [22], who pointed out the ability of willow extracts to modulate the gut microbiome, reducing systemic inflammation. However, this study is the first to directly compared the clinical efficacy of a standardised extract with a synthetic NSAID, bridging the gap between preclinical research and practical application. The work of E.L. Maistro *et al.* [23] confirmed the absence of hepato- and nephrotoxicity even at high doses of *Salix alba* extract (500 mg/kg) in rats, supporting the conclusions about the low incidence of side effects (10%) in clinical settings. The authors pointed to the antioxidant properties of the extract, which neutralise oxidative stress, explaining its protective effect on organs. These data are consistent with the observation of a 30% reduction in MMP-3, a marker of cartilage degradation, in the study.

A study by D. Ojeda-Ramirez *et al.* [24] found that *Salix babylonica* had a weaker effect on IL-6 compared to NSAIDs, which contradicts the results obtained for *Salix alba*. This difference may be explained by species characteristics (*Salix babylonica* contains less salicin and more tannins) or extraction methods: D. Ojeda-Ramirez *et al.* used aqueous extracts, while this study used a standardised ethanol extract with higher salicin bioavailability. The work of R. Carpa *et al.* [25] pointed to the selective antibacterial activity

of salicin isolated from *Salix alba*, which does not disturb the balance of beneficial bacteria in the intestine. This may explain the lower incidence of diarrhoea reported in the study, as preservation of the intestinal microbiome prevents dysbiosis, a common cause of gastrointestinal disorders. Unlike synthetic NSAIDs, which often inhibit the growth of *Lactobacillus* and *Bifidobacterium*, salicin selectively acts on pathogenic strains, as confirmed *in vitro*.

A study by S. Faid [26] demonstrated that *Salix* spp. leaf extract reduces TNF- $\alpha$  levels by 40% in rats with rheumatoid arthritis by inhibiting NF- $\kappa$ B activation, which is consistent with the 55% reduction in CRP reported in the present study. Unlike this study, which focused on chronic effects in osteoarthritis, S. Faid's study used a model of acute inflammation, highlighting the versatility of salicin. It is important to note that the use of the extract in S. Faid's study was localised, whereas this study demonstrated systemic efficacy. The study by H.N. Phillips *et al.* [27] demonstrated that oral willow extract does not lead to an increase in prostaglandin E2 levels in calves, unlike flunixin meglumine, which caused a significant increase in this marker of inflammation. These data are consistent with the results obtained regarding the lower incidence of side effects in the *Salix alba* group, since the inhibition of prostaglandin synthesis without COX-1 acetylation leaves the gastric mucosa intact. In addition, the lack of effect on prostaglandin E2 explains the preservation of the protective mechanisms of the mucosa, which is critical for the safety profile.

A study by K. Warmiński *et al.* [28] found high levels of flavonoids, particularly quercetin and rutin, in the bark of *Salix alba*, which explains the antioxidant activity of the extract ( $IC_{50} = 45 \pm 5 \mu\text{g/mL}$ ). These flavonoids have been shown to neutralise free radicals by donating electrons, which is consistent with the reduction in oxidative stress in synovial fluid observed in the study. Unlike other species of the genus *Salix*, *Salix alba* exhibits a higher concentration of polyphenols, making it a promising source for the development of antioxidant therapeutic agents. The work of J. Tienaho *et al.* [29] proved that *Salix* spp. polyphenols inhibit virus replication by blocking viral proteases, which expands the potential range of applications of extracts beyond anti-inflammatory therapy. Although the study did not analyse the effect on oxidative stress, the properties identified correlate with the ability of polyphenols to modulate cellular signalling pathways associated with the immune response. This highlights the versatility of willow's bioactive components, which can simultaneously affect different links in the pathogenesis. A study by L. Zheng *et al.* [30] demonstrated that polyphenolic beverages based on *Salix alba* have neuroprotective properties *in silico*, in particular by inhibiting beta-secretase associated with the development of Alzheimer's disease. These data confirmed the broad pharmacological potential of willow extracts, which is not limited to joint pathology. However, in the context of osteoarthritis, their effect on joint function is key, as evidenced by a 42% improvement on the WOMAC scale.

The work of D. Reshamwala *et al.* [31] showed that willow extracts had no effect on coronavirus replication, which contradicts their antiviral activity against other pathogens found in previous studies. This difference may be explained by the species specificity of bioactive components or the peculiarities of interaction with specific viral

proteins. In the context of osteoarthritis, such results emphasised that the therapeutic effect of extracts is primarily due to anti-inflammatory and antioxidant mechanisms, rather than direct antiviral action. A study by E. Gligorić *et al.* [32] found that the bioactive components of *Salix alba*, in particular salicin, selectively interact with pro-inflammatory cytokines (e.g., IL-1 $\beta$ ) without affecting the function of the intestinal epithelium. This explains the absence of toxicity and preservation of the structural integrity of the gastrointestinal tract in the extract group. These properties make *Salix alba* promising for long-term use, especially in patients with a sensitive digestive tract.

A study by I. Sharma *et al.* [33] demonstrated the efficacy of effervescent tablets based on *Salix alba* bark, where the standardised extract reduced CRP levels by 38% after 4 weeks of use. These results are consistent with data on a 42% reduction in pain syndrome on the WOMAC scale in the study group, which emphasises the importance of the pharmaceutical form for the bioavailability of salicin. Unlike this study, which used effervescent tablets, the study used encapsulated extract, which may have affected the rate of onset of the effect. The work of M. Neagu *et al.* [34] found that the bark of *Salix alba* contains 20-30% more phenolic compounds (salicin, quercetin) than the leaves and branches, which explains the higher antioxidant activity of extracts from this part of the plant. These data confirm the choice of bark as the main source of bioactive components in the study and also explain the reduction in oxidative stress in synovial fluid. However, the authors did not analyse the effect of phenols on joint function, which limits direct comparison with the WOMAC scale results.

A study by N.P.K. Le *et al.* [35] and I.K. Venger [36] showed that *Salix alba* bark extracts inhibit NF- $\kappa$ B activation 1.5-2 times more effectively than acetylsalicylic acid in models of SARS-CoV-2 and LPS-induced inflammation. This is consistent with data on a 58% reduction in IL-6 in the extract group, indicating the superiority of the multitasking action of natural compounds over synthetic NSAIDs. Unlike this study, which focused on the cytokine cascade, the study analysed clinical parameters, emphasising the need for a comprehensive approach to evaluating efficacy. A comparative analysis confirmed that *Salix alba* bark extracts are promising for the treatment of inflammatory diseases due to high content of phenolic compounds and multifaceted action. Discrepancies in the results are due to differences in pharmaceutical forms, standardisation methods and research models, which emphasises the need for further clinical trials to unify protocols.

These studies have highlighted the broad pharmacological potential of *Salix alba*, in particular its anti-inflammatory, antioxidant and immunomodulatory properties. Despite differences in approaches, studies and forms of administration, *Salix alba* has consistently demonstrated a positive effect on the course of pathological processes.

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This confirmed the feasibility of further research to expand the scope of clinical application and unify therapeutic approaches.

## ◆ CONCLUSIONS

The results obtained demonstrated that *Salix alba* extract is clinically effective in stage II-III osteoarthritis of the knee joint, showing similar symptom reduction results compared to ibuprofen. However, unlike the latter, white willow extract demonstrated a significantly better safety profile, making it a promising alternative in the long-term treatment of chronic inflammatory diseases of the musculoskeletal system. The results of the study confirmed that salicin, the main active component of *Salix alba* extract, acts as a prodrug, metabolising to salicylic acid, which, unlike acetylsalicylic acid, does not acetylate COX enzymes, reducing the risk of gastrointestinal complications. In addition to inhibiting COX-1/COX-2, the extract exerts its effect by suppressing NF- $\kappa$ B-dependent transcription of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ) and also demonstrates significant antioxidant activity (IC<sub>50</sub> = 45  $\pm$  5  $\mu$ g/mL), which has been confirmed by *in vitro* results.

In a clinical study involving 120 patients with osteoarthritis, the use of 240 mg of salicin daily for 12 weeks led to a 4.3 point reduction in pain syndrome according to the VAS and a 42% improvement in joint function according to the WOMAC scale. These results were comparable to those in the ibuprofen group, but the incidence of side effects in the extract group was significantly lower (10% vs 25%). Of particular importance is the fact that *Salix alba* therapy was accompanied by a 55% reduction in CRP levels and a 30% reduction in MMP-3 concentrations, indicating the potential to slow down cartilage degradation.

Thus, *Salix alba* bark extract is a multi-component agent with complex analgesic, anti-inflammatory and antioxidant effects, allowing it to influence both the symptoms and the pathogenetic mechanisms of osteoarthritis. The limitations of the study were the absence of a placebo group, the duration of the study (12 weeks) and the limited sample size (patients with knee osteoarthritis), which does not allow the results to be extrapolated to other inflammatory pathologies or to assess the long-term consequences. Further studies should include imaging methods (e.g., magnetic resonance imaging) to assess structural changes in cartilage under the influence of *Salix alba* extract.

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None.

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## Протизапальна активність екстракту кори верби (*Salix alba*) та його вплив на маркери запалення в організмі людини

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**Анотація.** Дослідження було спрямоване на оцінку протизапальної ефективності та безпеки екстракту кори *Salix alba* порівняно з ібупрофеном у пацієнтів із остеоартритом колінного суглоба. У 12-тижневому рандомізованому контрольованому дослідженні в Україні взяли участь 120 пацієнтів із діагнозом остеоартрит II-III стадії, розподілених на дві групи: перша отримувала стандартизований екстракт верби (240 мг саліцину на добу), друга – ібупрофен (1 200 мг/добу). Больові показники за візуально-аналоговою шкалою знизилися з  $7,4 \pm 1,2$  до  $3,1 \pm 1,5$  балів ( $\Delta = 4,3$ ;  $p < 0,001$ ) у групі *Salix alba* та з  $7,6 \pm 1,1$  до  $3,0 \pm 1,4$  балів ( $\Delta = 4,6$ ;  $p = 0,12$ ) у групі ібупрофену. Функція суглобів, оцінена за шкалою Western Ontario and McMaster Universities Osteoarthritis Index, покращилася на 42 % та 45 % відповідно ( $p = 0,24$ ). Рівень С-реактивного білка зменшився на 55 % проти 60 % ( $p = 0,18$ ), інтерлейкіну-6 – на 58 % проти 60 % ( $p = 0,29$ ), фактору некрозу пухлини- $\alpha$  – на 50 % проти 52 % ( $p = 0,41$ ). Побічні ефекти зареєстровані у 10 % пацієнтів групи верби проти 25 % у контролі, переважно шлунково-кишкового характеру. Виявлено помірну кореляцію між рівнем саліцину в крові та зниженням болю ( $r = 0,45$ ;  $p < 0,001$ ). Результати доводять, що екстракт *Salix alba* має аналогічну ібупрофену ефективність, але з меншим ризиком ускладнень завдяки багатозадачній дії (інгібування циклооксигеназ, модуляція цитокінів, антиоксидантний ефект). Отримані дані обґрунтовують використання екстракту як альтернативи синтетичним протизапальним засобам у клінічній практиці, особливо для пацієнтів із хронічними запальними захворюваннями, де тривалий прийом нестероїдних протизапальних препаратів супроводжується підвищеним ризиком побічних ефектів. Результати роботи можуть бути використані ревматологами та лікарями-терапевтами у клінічній практиці для призначення екстракту *Salix alba* як безпечної альтернативи нестероїдним протизапальним препаратам пацієнтам із остеоартритом

**Ключові слова:** фармакологія; ібупрофен; остеоартрит; С-реактивний білок; саліцилати