

Onosma Bracteatum Wall (Gojihva): A Promising Anti-Arthritic Herb

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Abstract: Persistent synovial inflammation, increasing cartilage degradation, bone erosion, and systemic consequences are the hallmarks of rheumatoid arthritis (RA), a chronic autoimmune inflammatory disease. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) are examples of conventional therapies that effectively control the progression of the disease, but their long-term use is frequently linked to side effects, high treatment costs, and inconsistent patient response. Finding therapeutic compounds derived from plants with enhanced safety and multi-target pharmacological efficacy is therefore of growing interest. Wall Onosma bracteatum. (Boraginaceae), sometimes referred to as Gojihva, is a significant medicinal plant used to cure inflammatory conditions and other illnesses in Ayurvedic and Unani medical systems. The information on O. bracteatum's botanical traits, phytochemical makeup, traditional medicinal applications, pharmacological activity, and anti-arthritic potential is compiled in this review. Flavonoids, phenolic acids, naphtho quinones, alkaloids, tannins, and other bioactive components with immune modulatory, anti-inflammatory, and antioxidant qualities are abundant in the plant. Significant free radical scavenging action, lipoxygenase inhibition, and human red blood cell membrane stability are shown in experimental experiments, indicating possible mechanisms for reducing oxidative stress and inflammation linked to rheumatoid arthritis. The paper also covers pharmacokinetic information gaps, standardization issues, quality control methods, phytosomes, liposomes, polymeric nanoparticles, and transdermal delivery systems as potential formulation options. All things considered, O. bracteatum is a promising natural candidate for the creation of cutting-edge anti-arthritic medications. To determine its safety, effectiveness, and therapeutic applicability, however, randomized clinical trials, standardized formulations, pharmacokinetic studies, and well-designed in vivo studies are crucial.

Keywords: Onosma bracteatum, Gojihva, Boraginaceae, rheumatoid arthritis, anti-inflammatory, antioxidant, phytochemicals, pharmacology, lipoxygenase inhibition, HRBC membrane stabilization, toxicity, pharmacokinetics, nanoparticles, phytosomes.

1. Introduction

Burden of Rheumatoid Arthritis: A system immune disease linked to a persistent inflammatory process, rheumatoid arthritis (RA) can harm extra-articular organs such as the heart, kidney, lung, digestive system, eye, skin, and neurological system in addition to joints. In order to categorize various forms of arthritis into non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis caused by crystal deposition (pseudo-gout, basic calcium phosphate disease, gout), bacterial and viral infections (Staphylococcus-aureus, Neisseria-gonorrhea, complications of Lyme disease, Parvo virus, Enterovirus), or autoimmune processes. The diagnosis of rheumatoid arthritis is primarily, with pain, stiffness, and swelling of multiple joints in a bilateral, symmetric pattern. A minority of patients present with oligo-articular asymmetric involvement. The onset is usually insidious, with joint symptoms emerging over weeks-months and often accompanied by anorexia, weakness, or fatigue. Patients usually note morning stiffness lasting more than an hour.

Limitations of current Rheumatoid Arthritis therapy: Since RA is a diverse chronic illness, there isn't a one treatment that works consistently and universally for every patient. Additionally, bDMARDs and tsDMARDs exhibit this. When RA is treated with bDMARDs or tsDMARD, it is challenging to forecast clinical outcomes. Some patients are difficult to treat and do not reach the treatment targets as clinical remission or low disease activity. Known negative prognostic factors, such as the presence of auto-anti-bodies and joint erosion, the presence of a genetic profile, comorbidities and extra-articular manifestations, pregnancy or a pregnancy wish may concur to the treatment failure. In this research, we sought to identify RA patients who are challenging to treat and to identify the best pharmacological and environmental targets. Joint injury is correlated variably with genetic markers of severity such as HLA-DRB1, TRAF1, PSORS1C1, and micro-RNA 146a. Physical activity, cocoa, curcumin, minimal salt intake, and a Mediterranean diet all appear to have positive effects; however, further research is needed to determine dosage, safety, and effectiveness in RA.

2. Botanical profile of onosmabracteatum:

Taxonomy: The genus *Onosma* L. (Boraginaceae) has approximately 150 species that are known to exist throughout Asia, including 29 species in China, 95 species in Turkey, and 8 species in Pakistan. However, the number of species in this genus has expanded to over 230 as a result of current research and revisions. Linnaeus established the term *onosma* for this genus into contemporary botanical taxonomy. The Latin word "osma" comes from a Greek word that signifies "smell." All species, sometimes referred to as rock garden plants, thrive in dry or wet, sunny environments, typically in rock fissures. *Onosma Helvetica* (A.DC.) is one of two uncommon species of *Onosma* that live in calcareous steppe meadows in Switzerland. The second is *Onosma pseudoarenaria* Schur, which is dispersed over central Valais, and Boissier, which is situated in Ollon (VD) and Haut Valais.

Vernacular names:

Language	Name
Hindi	Rtanjotjoshi, Gaujaban, Gojiva
Odia	Kharsan, Kharapatra
Kannada	ShankhaHuli, Aakalanalige, Gojada
Punjabi	Kazban
Urdu	Gaozaban
English	Vipersbugloss
Middleeastcountries	Gaozaban
Arabic	Lisam-al-Thawa or Saqill-ul-Hammam

Table: 1

3. Geographical distribution:

At elevations of 3,500–4,500 meters, *O. bracteatum* is sparingly scattered throughout the North Western Himalayas, from Pakistan's Swat to the Kumaon region of India and Nepal. According to reports, the plant is also present in Iran, Pakistan, and Nepal. Fig. highlights the plant distribution based on ENVIS, www.gbif.org, and other reports. In Pakistan, it may be found in Baluchistan, Swat, Chaman, Chitral, Kalam, Dir, Parachinar, and Kaghn regions; in India, it can be found in Jammu and Kashmir, Himachal Pradesh, and Uttarakhand.

4. Traditional medicinal uses:

Term	Uses
Grahi	Absorbent, diarrhoea
Hrudya	Cardiotonic-heart health, congenital heart disorders
Hima	Coolant-reduces body heat

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Shwasa	Respiratory support-Asthma disorders, chronic respiratory disorders
Kasa	Relieves cough and cold
Anichi	Improves appetite-anorexia(loss of appetite)
Vrana	Wound healing-Ulcers,wounds
Prameha	Urinary tract disorders, diabetes

Table:2

Morphological characteristics: **Habit**- small, erect, perennial herb, **Root**-Tap root, thick & woody; **Stem**-green, branched, covered with rough hairs; **Leaves**- simple, alternate, narrow, hairy, without stalk; **Inflorescence** – cluster of flowers with leafy bracts; **Flowers** – small, tubular, bell shaped, pale-white, bisexual; **Calyx** -5 sepals, hairy, fused at the bases; **Corolla**- 5 fused petals forming a tube; **Stamens**- 5 stamens attached to the corolla tube **Ovary** – superior, divided into 4 lobes; **Fruit**- 4 small nutlets; **Seed**- small,hard,1seed in each nutlet.

Microscopic characteristics: **Epidermis**-single layer of cells covered with a cuticle, bears numerous hairs; **Trichomes** - long, multicellular, uniseriate, rough & stiff hairs. **Mesophyll**- differentiated into palisade and spongy parenchyma; **Palaside tissue**- 1 layer of elongated, chlorophyll containing cells beneath the upper epidermis; **Spongy parenchyma**-loosely arranged cells with air spaces. **Vascular bundle**-collateral and closed, contain xylem and phylum; **Xylum**-well developed vessels and xylem fibers; **Phylum**- composed of sieve tubes, companion cells and phylum parenchyma. **Calcium oxalate crystals** - present in parenchyma cells; **Stomata**- mainly present on the lower epidermis.

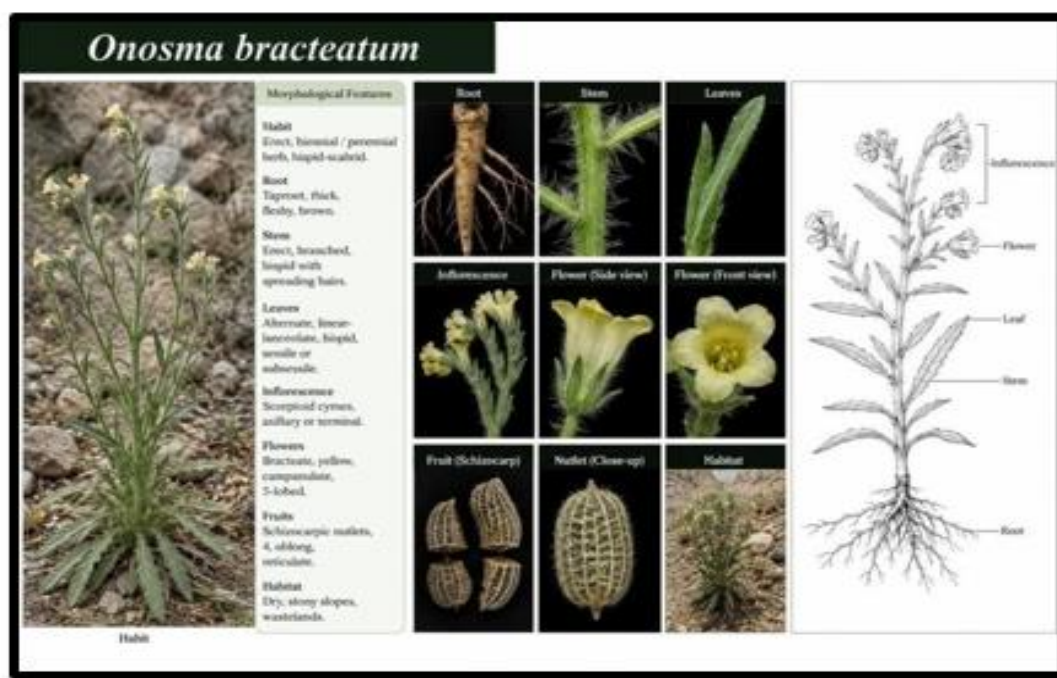


Fig: 1

Phyto -chemical constituents:

Plantpart	Phytoconstituentspresent
Aerial parts	Glycosides, alkaloids, saponins, steroids, coumarins
Leaves	Saline mucilage, pyrrolizidine alkaloids
Stem	Saline mucilage
Seeds	Proteins, fixed oils
Flowers	Choline, glucose, fructose, amino acids, tannins
Fruits	Alkaloids, glycosides, steroids, terpenes, saponins, tannins

Table :3

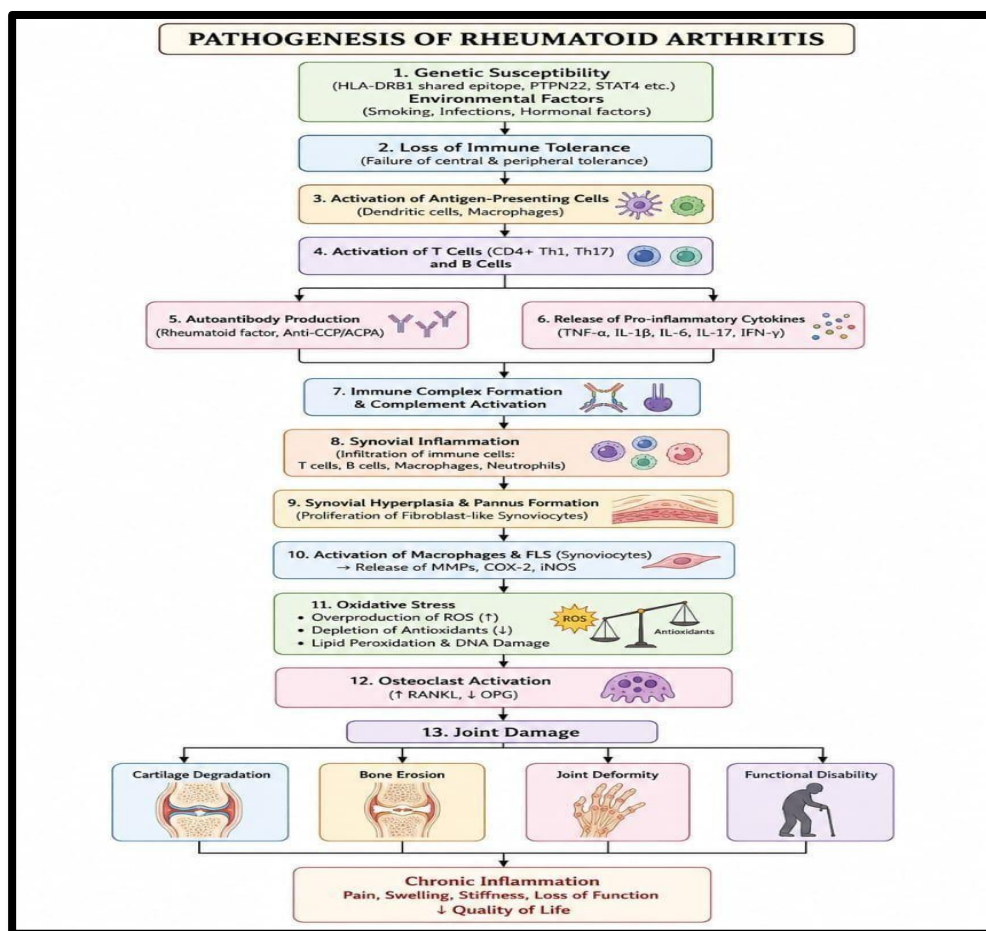


Fig: 2

5. Experimental evidence of Anti-arthritic activity:

Anti-oxidant activity study on Onosmabracteatum:

Because *Onosma bracteatum* Wall. is rich in phenolics, flavonoids, tannins, naphthoquinones, and phenolic acids, it has strong antioxidant action. These substances neutralize reactive oxygen species (ROS) and may lessen oxidative stress linked to long-term conditions like diabetes, cancer, heart disease, and neurological disorders^[11] Strong antioxidant activity has been shown in vitro utilizing DPPH, nitric oxide, ABTS, and reducing-power tests, especially in methanolic and ethanolic extracts. With an IC_{50} of 21.76 μ g/ml, a methanolic leaf extract demonstrated 85.46% DPPH radical scavenging activity, which is similar to ascorbic acid (IC_{50} = 18.21 μ g/ml). Gallic acid and quercetin were found to be significant antioxidant components by HPLC investigations. Although more in vivo and clinical research is required to validate its therapeutic potential, reviews of the *Onosma* genus also identify *O. bracteatum* as a medicinally significant species with a high phenolic content.

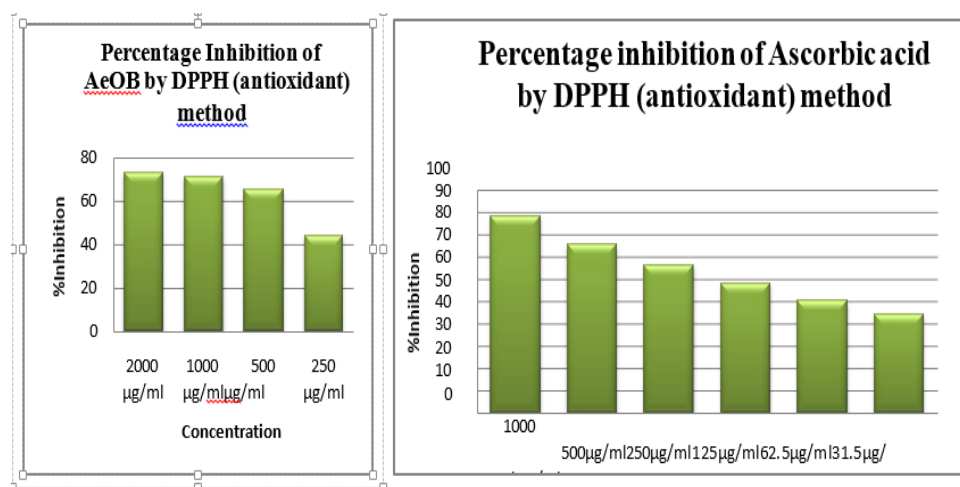


Fig: 3, Fig: 4

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Lipoxygenase (LOX) Inhibition Assay: Poly unsaturated fatty acids like linoleic and arachidonic acids are oxidized by non-heme iron-containing enzymes known as lipoxygenases (LOXs; EC 1.13.11.12) to create inflammatory mediators associated with inflammatory illnesses like cancer, asthma, and arthritis. Therefore, a key indicator of the ability of medicinal herbs to lower inflammation is LOX inhibition. The ferrous oxidation– xylene orange (FOX) assay, which gauges the production of lipid hydro-peroxide during linoleic acid oxidation, is frequently used to assess LOX inhibitory activity. This procedure involves incubating plant extracts with LOX and linoleic acid before adding FOX reagent. Fe^{2+} is oxidized to Fe^{3+} by the produced hydro-peroxides, resulting in a colorful complex with xylene orange that can be detected spectrophotometrically at 560 nm. While suitable blanks and negative controls take environmental interference into account, quercetin is typically utilized as a positive control. The absorbance values of the control and sample reactions are used to compute the % inhibition of LOX activity. $\text{LOX Inhibition (\%)} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$ where A_{sample} is the absorbance in the presence of the test extract and A_{control} is the absorbance of the control reaction. A larger percentage inhibition indicates that the plant extract under study has greater anti-inflammatory potential due to its superior LOX inhibitory action.

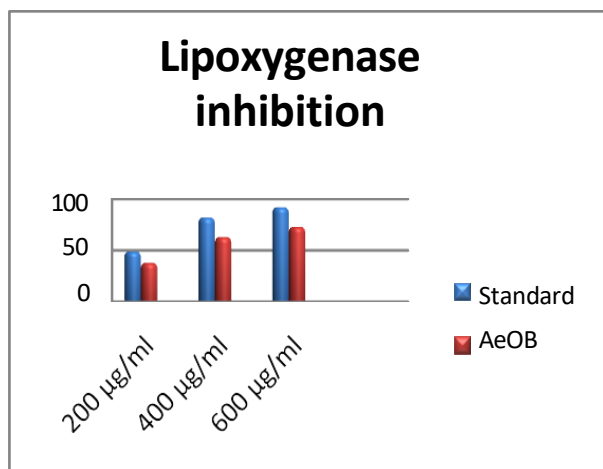


Fig.5

Human Red Blood Cell (HRBC) Membrane Stabilization Assay: The plant extract's in vitro anti-inflammatory efficacy was assessed using the HRBC membrane stabilization method. An identical volume of Alsever's solution was combined with blood, and the mixture was centrifuged at 3000 rpm. After being cleaned with 0.9% NaCl, the packed erythrocytes were made into a 10% HRBC suspension. Phosphate buffer, hyposaline, and HRBC suspension were combined at extract quantities ranging from 10 to 500 µg/ml, and the mixture was incubated for 30 minutes at 37°C. Hemoglobin release was measured spectrophotometrically at 560 nm following centrifugation. An extract-free sample served as the control, and the standard was Indomethacin (100 µg/ml). The following formula was used to determine the percentage of HRBC membrane stabilization:

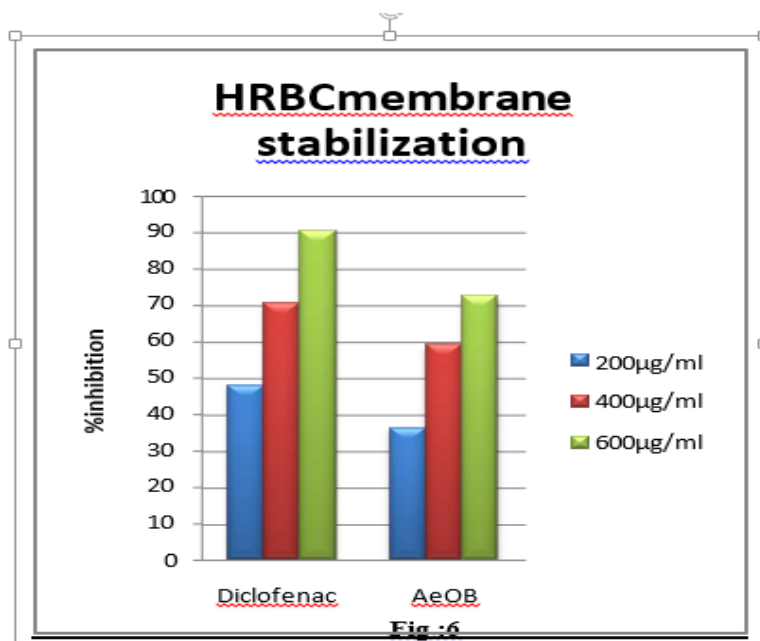


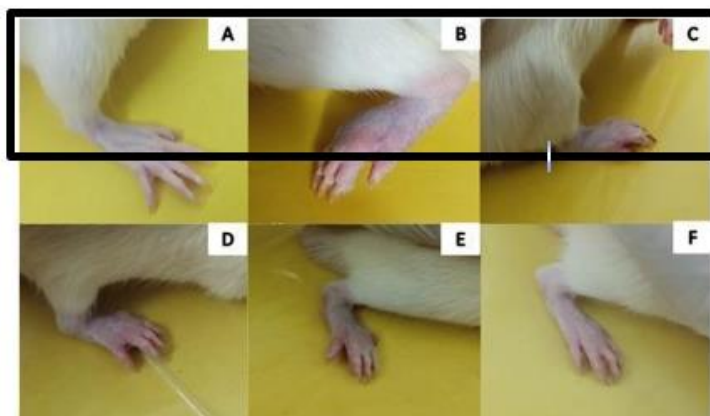
Fig. 6

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%Protection is equal to $100 - [(OD \text{ of treated sample} / OD \text{ of control}) \times 100]$. Because erythrocyte membranes and lysosomal membranes are physically similar, membrane stabilization is that to be a sign of possible anti-inflammatory action, which is why the assay is frequently employed to screen for anti-inflammatory activity. Human erythrocytes are exposed to heat or hypotonic stress when plant extracts are present. Membrane damage causes hemoglobin leakage, which can be measured spectrophotometrically at 560 nm. Plant extracts with membrane-stabilizing qualities reduce hemolysis. The following formula is used to calculate hemolysis inhibition as a percentage: %Inhibition = $[(\text{Absorbance of Control} - \text{Absorbance of Sample}) / \text{Absorbance of Control} \times 100]$. Higher inhibition is a sign of stronger anti-inflammatory potential. Method of **Human RBC Assay**: In the 2024 study published in *Molecules*, the aqueous-ethanolic extract of *O. bracteatum* was evaluated using the following method. Fresh blood obtained from a healthy donor with ethical approval. Regular saline was used to clean the RBCs. 10% RBC suspension prepared in phosphate buffer with a pH of 7.4. Equal volumes of extract and RBC suspension were mixed together. Examined extract concentrations were 200 µg/ml, 400 µg/ml, and 600 µg/ml. 50°C incubation for 25 minutes. Centrifugation at 2500 rpm for five minutes. At 560 nm, the supernatant's absorbance was measured. Diclofenac sodium is a common anti-inflammatory drug.

Complete Model Paw Diameter Induced by Freund's Adjuvant:

When compared to Group-VI (AeOB, 750 mg/kg) and Group-III (indomethacin, 10 mg/kg), the arthritic control group (Group-II) showed signs of severe CFA-induced arthritis. All groups, with the exception of Group II, showed a decrease in the arthritic phase between days 12 and 28. When compared to the other treatment groups, Group II showed the most decrease in paw diameter. However, Group-VI's (AeOB, 750 mg/kg) outcome was similar to Group-III's because



Fig, 7

An example of a rat paw caused by CFA on day 28:

**Group I (normal),
Group II (arthritic control), Group III (standard),
Group IV (AeOB, 250 mg/kg), Group V
(AeOB, 500 mg/kg), Group VI (AeOB, 750 mg/kg)**^[5]

Safety and toxicological considerations: Acute toxicity: Oral doses of 5–20 mg/kg and intra-peritoneal doses up to 10 g/kg caused no mortality or obvious toxicity in rats. 14-day observation: No delayed toxic effects were observed during this period. Oral doses ranging from 50 to 750 mg/kg were well tolerated with no reported acute adverse effects.

Sub acute / chronic toxicity: *Onosma bracteatum* extracts were well tolerated with no mortality or significant toxicity at tested doses. No toxicity observed up to 10 g/kg intra-peritoneally; oral doses of 5–20 mg/kg were also non-toxic. No major adverse effects reported at therapeutic doses, though long-term toxicity data remain limited.

Standardization Challenges in *Onosma bracteatum* : Phytochemical Variability : *Onosma bracteatum* (Gojihva) exhibits significant variation in its phytochemical content due to a combination of environmental, genetic, developmental, and methodological factors. Key influences include altitude, temperature, rainfall, soil composition, light exposure, geographical origin, the specific plant part used, harvesting season, and extraction methods. Environmental stresses can elevate levels of phenolics and flavonoids, which poses challenges for the standardization of herbal formulations based on this plant.

Variation among Plant Organs: Leaves are rich in phenolics, flavonoids, and tannins. Roots contain higher levels of naphtha quinone derivatives like alkannin and shikonin analogues. Flowers and stems have unique metabolite profiles, contributing differently to pharmacological effects.

Need for Quality Control: Due to the above factors, bioactive compound concentrations vary widely, causing inconsistent therapeutic effects and complicating quality standards. Comprehensive phytochemical profiling is essential to reduce batch-to-batch variability.

Marker-Based Standardization: This approach ensures herbal drug identity, purity, consistency, and efficacy by quantifying specific marker compounds. It is especially important for *O. bracteatum* due to its phytochemical variation and frequent adulteration with related species. Currently, there is no official pharmacopoeial marker for this plant.

Analytical Techniques for Marker-Based Standardization: High-Performance Liquid Chromatography (HPLC) is the preferred technique because it offers: High sensitivity, excellent reproducibility, Accurate quantification of phenolic acids and flavonoids, Reliable batch-to-batch comparison.

Challenges in Market-Based Standardization: Absence of an official marker compound; Significant phytochemical variation due to region and season; Frequent adulteration and substitution of raw materials; Limited validation of proposed marker compounds; Lack of a standardized extraction method; Weak correlation between marker compounds and therapeutic efficacy.

6. Future Formulation Perspectives:

Nano formulations : Polymeric nano particles , Solid lipid nano particles (SLNs) ,Nano structured lipid carriers (NLCs) , Liposomes ,Nano emulsions ,Nano micelles , Dendrimers .Nanocarriers can enhance targeted delivery of *O. bracteatum* phytochemicals while minimizing systemic toxicity . Nano formulations should be standardized using key marker compounds such as rosmarinic acid, caffeic-acid, chlorogenic-acid, ferulic-acid, apigenin, luteolin, and shikonin derivatives. Combinational nanotherapy holds potential to overcome multi drug resistance in cancer and microbial infections. Future research directions include exploring nano-emulgels, nano-hydrogels, nano-fibers, and transdermal patches for wound healing and anti-inflammatory treatments. Advanced delivery systems like mucoadhesive nanoparticles, gastro-resistant nano-capsules, and self-nanoemulsifying drug delivery systems (SNEDDS) may enhance gastrointestinal absorption and oral bioavailability.

Phytosomes: Utilizing standardized extracts and important marker chemicals, create *O. bracteatum* phytosomes. Use DoE and QbD to optimize formulations for improved uniformity and quality. Phytosomes may enhance therapeutic efficacy, bioavailability, and skin penetration. Optimize drug release, phospholipid ratio, entrapment efficiency, zeta potential, and particle size using AI and machine intelligence.

Liposomes : Create liposomal gels, creams, hydrogels, nano-emulgels, and transdermal patches with antibacterial, anti-inflammatory, and wound-healing properties. While lowering systemic exposure, liposomes can enhance skin penetration, local retention , and prolonged activity. Co-encapsulation with anti-inflammatory, anti-cancer, or antibiotic medications may improve synergy, lessen adverse effects, and aid in overcoming multidrug resistance.

Polymeric Nanoparticles (PNPs): PNPs provide targeted delivery, controlled release, high drug loading, biocompatibility, and biodegradability. For better phyto chemical distribution, investigate polymers such PLGA, PLA, PCL, chitosan, alginate, gelatin, dextran, and Eudragit ®. Create polymer-lipid hybrid and stimuli-responsive nanoparticles for sophisticated medication delivery. Prior to clinical usage, standardize characterisation and quality-control techniques and conduct long-term safety investigations.

Transdermal Approaches: Phytochemicals can be delivered via targeted nanocarriers to tumors, wounds, infections, and inflammatory skin. Antibodies, peptides, folic acid, and HA may enhance cellular absorption and targeting. Combination therapy may lower dosages and adverse effects while improving efficacy.

7. Research Gaps in Onosma bracteatum Pharmacokinetics (PK):

Pharmacokinetic Gaps: There aren't enough thorough in vivo PK(ADME) investigations in humans or animals. There is a lack of important information on bioavailability, absorption, distribution, clearance, half-life, metabolism, and excretion. Instead of PK trials, the majority of current research focuses on phytochemical isolation and pharmacological effects. **Indirect PK Evidence:** 37 phytochemicals have been found, offering possible subjects for upcoming PK investigations. Absorption: No information on oral bioavailability or gastrointestinal absorption is available. Distribution: Organ accumulation, protein binding, and tissue distribution are still unknown. Metabolism: It is unknown what metabolite profiles, CYP450 interactions, and metabolic pathways are Excretion: There are no species-specific statistics on biliary or urine elimination.

Future Directions: Perform thorough in-vivo ADME/PK investigations. •Assess tissue distribution, absorption, plasma profiles, and oral bioavailability. • Research excretion, CYP450 interactions, metabolism, and protein binding. • For in-depth PK research, look into important bioactive substances, particularly benzoquinones. • The clinical development and therapeutic application of *O. bracteatum* depend on these investigations. Conclusion:

Because *Onosma bracteatum* contains flavonoids, phenolic acids, naphtha-quinones, and alkaloids that exhibit immuno-modulatory, anti-inflammatory, and antioxidant properties, it is a promising therapeutic plant for rheumatoid arthritis. Its ability to lessen oxidative stress, inflammation, and tissue damage is supported by in vitro and early animal research. However, the paucity of clinical trials, pharmacokinetic and toxicological investigations, and standardized extracts continue to limit the evidence. Additionally, phytochemical variance emphasizes the necessity of marker-based standardization and quality control. In vivo investigations, pharmacokinetics, long-term safety, molecular mechanisms, and randomized clinical trials should be the main topics of future research. Phytosomes, liposomes, nanoparticles, nanoemulsions, and transdermal formulations are examples of advanced delivery systems that may increase bioavailability and efficacy.

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