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A PHARMACOLOGICAL REVIEW OF *RANUNCULUS SCELERATUS* L.: PHYTOCHEMISTRY, PHARMACOLOGICAL ACTIVITIES

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ABSTRACT: *Ranunculus sceleratus* L. belongs to the family Ranunculaceae and is an annual herb widely distributed in moist habitats, including ditches, slow-moving streams and shallow ponds. The plant has a long history of use in traditional medicine, particularly in Asian traditional medical systems, where it has been employed for inflammatory disorders, skin conditions, rheumatic complaints, jaundice and other ailments. However, the fresh plant is toxic and contains irritant constituents associated with the ranunculin protoanemonin anemonin chemical system. Modern pharmacological investigations have provided evidence supporting several biological activities of *R. sceleratus*, including anti-inflammatory, hypotensive, antimicrobial, antifungal and hepatobiliary effects. Phytochemical investigations have identified flavonoids, phenolic acids, coumarins, lignans, nitrogen-containing compounds, anthraquinones, sterols and lactone derivatives. A UHPLC-Q-Orbitrap HRMS investigation characterized 69 compounds in an 80% methanolic extract, substantially expanding the known chemical profile of the species. Experimental studies have demonstrated modulation of inflammatory mediators, inhibition of eicosanoid production, reduction of blood pressure and improvement of experimentally induced intrahepatic cholestasis. More recent phytochemical work has isolated previously undescribed benzopyran derivatives with inhibitory effects on nitric oxide and pro-inflammatory cytokines in macrophage cells. Despite these promising findings, most evidence remains preclinical, and standardized preparations, pharmacokinetic studies, dose-response investigations and clinical trials are lacking. Furthermore, the toxicity of the fresh plant, particularly because of protoanemonin, requires careful consideration. This review summarizes the botanical background, traditional uses, phytochemical constituents, pharmacological activities, mechanisms, toxicological considerations and research gaps associated with *R. sceleratus* and evaluates its potential as a source of pharmacologically active natural products.

INTRODUCTION: Medicinal plants have historically provided important sources of therapeutic agents and continue to attract considerable scientific interest because of their structural diversity and broad biological activities.

The genus *Ranunculus* L., belonging to the family Ranunculaceae, comprises approximately 600 species distributed across different geographical regions.

Several species of the genus have been used in traditional medicine and investigated for antimicrobial, antioxidant, anti-inflammatory, immunomodulatory and other pharmacological activities¹. *Ranunculus sceleratus* L., commonly known as celery-leaved buttercup, is an annual herb associated particularly with wet and mineral-rich



environments. It occurs in slow streams, ditches and shallow muddy-bottomed ponds. Historical records indicate its use in traditional medicinal practices, particularly in Asian traditional medicine. The pharmacological importance of *R. sceleratus* is unusual because its medicinal and toxicological properties are closely interconnected. Fresh plant material contains ranunculin-related compounds that can generate protoanemonin, a potent irritant and blistering compound. Protoanemonin is unstable and can dimerize to form anemonin. Consequently, the pharmacological evaluation of this species must consider not only its potentially beneficial biological activities but also its toxicological profile ².

Scientific investigations conducted during the past several decades have reported anti-inflammatory, antimicrobial, antifungal, hypotensive and hepatobiliary effects of *R. sceleratus*. More recent chemical investigations have considerably expanded the known phytochemical profile of the plant, while isolation of new benzopyran derivatives has provided additional evidence for its anti-inflammatory potential ³.

The purpose of the present review is therefore to critically summarize the available evidence concerning the traditional uses, phytochemistry, pharmacological activities, possible mechanisms of action and toxicity of *R. sceleratus*, with particular emphasis on experimentally demonstrated effects rather than traditional claims alone.

Botanical and Taxonomical Description:

Taxonomy:

Taxonomic rank	Classification
Kingdom	Plantae
Family	Ranunculaceae
Genus	<i>Ranunculus</i>
Species	<i>Ranunculus sceleratus</i> L.

R. sceleratus is an annual herbaceous species. Its preference for wet habitats distinguishes it ecologically from many terrestrial members of the genus. The species is distributed across several regions and has been recorded in traditional medical systems in Asia ⁴.

Morphological Characteristics: The plant is characterized by an herbaceous growth habit and leaves that contribute to its common description as

celery-leaved buttercup. As with other members of *Ranunculus*, its identification should be based on botanical characteristics and authenticated plant material when used for pharmacological or phytochemical research.

For experimental studies, proper taxonomic authentication and deposition of a voucher specimen are particularly important because the genus contains numerous species with overlapping traditional applications and potentially different chemical profiles.

Traditional and Ethnomedicinal Uses: Historical evidence indicates that *R. sceleratus* has been used medicinally for a variety of conditions. Traditional Chinese medical records associate the plant with applications including lower-extremity ulcers, rheumatic joint pain, snakebite-related sores and hypertension. The species has also been associated with traditional approaches to jaundice and hepatobiliary disorders ⁴.

An unusual traditional application involves Tian Jiu therapy, in which fresh *R. sceleratus* is applied as an herbal patch to selected acupuncture points. The irritant effect of the fresh plant produces local hyperemia and blistering. Experimental research subsequently investigated whether this traditional procedure could influence experimentally induced intrahepatic cholestasis ¹.

However, traditional use should be regarded as a rationale for investigation rather than proof of therapeutic efficacy. The strongest conclusions concerning *R. sceleratus* should therefore be based on controlled pharmacological and experimental studies.

Phytochemical Constituents: The pharmacological properties of *R. sceleratus* are likely related to a chemically diverse collection of secondary metabolites.

Earlier phytochemical studies identified compounds including:

- ❖ β-sitosterol
- ❖ stigmasterol
- ❖ stigmasta-4-ene-3,6-dione

- ❖ isoscopoletin
- ❖ scoparone
- ❖ protocatechuic aldehyde
- ❖ protocatechuic acid
- ❖ phenolic constituents
- ❖ lactone derivatives

Six compounds, including stigmasta-4-ene-3,6-dione, stigmasterol, isoscopoletin, scoparone, protocatechuic aldehyde and protocatechuic acid, were isolated and structurally characterized from the herb of *R. sceleratus*⁵.

Gao et al. (2005) isolated Six compounds from the herb of *R. sceleratus* and purified by extraction and different kinds of column chromatography. The structures were elucidated as stigmasta-4-ene-3, 6-dione I, stigmasterol II, isoscopoletin III, scoparone IV, protocatechuic aldehyde V and protocatechuic acid VI, respectively⁶.

Mahran et al. (1968) reported the presence of protoanemonin, anemonin and ranunculin in *Ranunculus sceleratus*⁷.

Misra and Dixit (1979, 1980) discovered that protoanemonin and anemonin extracted from *R. sceleratus* leaves had a strong antimicrobial function. Protoanemonin, is a volatile, oily, irritant substance. Protoanemonin has high affinity for SH groups⁸.

The stems of *R. sceleratus* contain numerous flavonoids, which were identified. It is well-known that flavonoids compound, which are important secondary metabolites in plants, have many roles in fat reduction, anti-thrombotic and anti- arrhythmic therapy, and as antioxidants⁹.

Dong et al. (2007) discovered that Tricin is a functional component in most types of buttercups and it was detected in *R. sceleratus*. Tricin has a potent resistance to exterior oxidation and it can be used to treat cancer in humans¹⁰.

Li et al. (2005) reported Apigenin 4'-O- alpha-rhamnopyranoside, apigenin 7- O- beta-glucopyranosyl-4'-O-alpha-rhamnopyranoside, tricin 7-O-beta-glucopyranoside, tricin, and

isoscopoletin and have been evaluated antiviral activity in *Ranunculus sceleratus*¹¹.

Pant M.C (1965), reported the presence of tryptamine derivative in *Ranunculus sceleratus* which is 5-hydroxy tryptamine¹².

Pharmacological Activities:

Anti-inflammatory Activity: Anti-inflammatory activity represents one of the best investigated pharmacological properties of *R. sceleratus*.

The aerial part of *Ranunculus sceleratus* has anti-inflammatory properties. It has been examined in rat's *in-vivo* and *in-vitro*. Later it is found that non-polar extract was able to inhibit eicosanoid production whereas polar extract enhances the synthesis of 5(S)- HETE, LTB4 AND 12(s)-HHTre¹³.

Prieto et al. investigated aerial-part extracts using several experimental models of acute and delayed inflammation, including carrageenan-induced paw edema, tetradecanoylphorbol acetate-induced inflammation and arachidonic-acid-related inflammatory models. The extracts produced anti-inflammatory or neutral effects *in-vivo*. *In-vitro* studies further demonstrated that non-polar extracts could inhibit eicosanoid production¹.

Interestingly, the response depended on extract polarity. Non-polar fractions inhibited certain inflammatory mediators, whereas polar extracts increased the synthesis of some eicosanoids, including 5(S)-HETE and LTB₄. These findings indicate that *R. sceleratus* contains both potentially anti-inflammatory and pro-inflammatory constituents and highlight the importance of extract composition¹.

Recent Evidence: A 2023/2024 phytochemical study isolated two previously undescribed benzopyran derivatives, ranunsceloside A and ranunsceloside B, along with two known coumarins. All four compounds inhibited LPS-induced production of NO, TNF- α , IL-1 β and IL-6 in RAW 264.7 macrophages in a concentration-dependent manner¹⁴.

This finding is important because it links specific isolated constituents with an experimentally

measurable anti-inflammatory effect rather than attributing activity only to a crude plant extract.

Antibacterial Activity: Antibacterial activity has been reported against five bacterial strains by 96-wells microplate assay using ciprofloxacin, a standard antibiotic. Chloroform, ethyl acetate, n-butanol and aqueous extract showed excellent activity against *Pseudomonas aeruginosa*, (MIC at 7.1, 7.8, 5.6 and 5.3 respectively), which is greater than standard antibiotic ciprofloxacin (MIC 10.0)¹⁵.

Antimicrobial and Antifungal Activity: The lactone derivatives associated with *Ranunculus* species have been reported to exhibit antimicrobial and fungicidal activities. Protoanemonin has particularly attracted attention because of its biological reactivity.

An *in-vitro* study specifically evaluated *R. sceleratus* against dermatophytes including *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum gypseum* and *M. fulvum*. Chloroform and methanol extracts showed greater antifungal activity than aqueous extracts, with reported MIC values for the organic extracts ranging from 1.25 to 10 mg/mL².

Antioxidant Activity: It has been determined the Ethyl acetate soluble fraction of this plant has great potential. It exhibited highest percent inhibition of DPPH radical. It showed $80.9 \pm 1.2\%$ inhibition of DPPH radical at a concentration of 30 µg/ mL. These results suggest that *R. sceleratus* is a valuable herb, which inhibits the oxidative stress mechanism that lead to degenerative diseases¹⁵.

Antidermatophytic Activity: It has been reported that *in-vitro* antidermatophytic activity in *Ranunculus sceleratus*. The chloroform extract exhibited the maximum activity with a halo of 23 mm diameter inhibition against *T. mentagrophytes* followed by *T. rubrum* (22 mm), *M. fulvum* (21 mm), *M. gypseum* (18 mm), and *T. tonsurans* (15 mm). The methanol extracts produced inhibition zone of 21, 16, 17, 17 and 10 mm respectively for *T. mentagrophytes*, *M. gypseum*, *T. rubrum*, *M. fulvum* and *T. tonsurans*¹⁶.

Antihypertensive Activity: The antihypertensive potential of *R. sceleratus* has been investigated

experimentally in normotensive and fructose-induced hypertensive rats.

The aqueous fraction produced notable hypotensive effects. Mechanistic investigations suggested involvement of several pathways, including:

- ❖ Muscarinic receptor activity;
- ❖ Angiotensin-converting enzyme inhibition;
- ❖ Ganglionic blockade;
- ❖ Nitric oxide release.

The involvement of several cardiovascular pathways is pharmacologically interesting because it suggests that the activity may not depend on a single molecular target⁴.

Hepatobiliary and Anti-cholestatic Activity: Zhang *et al.* investigated therapy using fresh *R. sceleratus* in rats with α -naphthyl isothiocyanate-induced intrahepatic cholestasis. Treatment reduced elevated serum AST, ALT, ALP, direct bilirubin, total bilirubin and total bile acid levels. Improvements were also observed in hepatic malondialdehyde, nitric oxide, bile flow and histopathological changes.

The authors proposed that the effect could be associated with attenuation of oxidative stress in liver tissue. GC-MS analysis identified 31 compounds, including lactones, flavonoids and phenolic acids. Importantly, protoanemonin content was approximately 25-fold higher in fresh material than in dried material in that study¹⁷.

This finding demonstrates how plant processing can substantially alter chemical composition and potentially biological activity.

Antioxidant Activity: The presence of flavonoids, phenolic acids and other polyphenolic constituents provides a plausible chemical basis for antioxidant effects. The broader *Ranunculus* literature documents antioxidant activities among several species, and *R. sceleratus* has been included in pharmacological investigations of the genus³. However, antioxidant capacity measured using chemical assays should not automatically be interpreted as evidence of antioxidant therapeutic efficacy in humans.

Future studies should therefore connect antioxidant assays with cellular, animal and pharmacodynamic outcomes.

Antiviral Potential: Some compounds isolated from *R. sceleratus* have demonstrated inhibitory activity against hepatitis B virus-related experimental systems. Reported compounds include sapigenin 4'-O- α -rhamnopyranoside, apigenin glycosides, tricin derivatives, tricin and isoscopoletin¹⁷.

Li, H.B et al. *Ranunculus sceleratus* has been reported for inhibitory effects on hepatitis B virus (HBV) and Herpes simplex virus type-1 (HSV-1)¹⁸.

This observation provides a possible explanation for some traditional hepatobiliary applications, but further mechanistic and *in-vivo* studies are required before antiviral therapeutic claims can be made.

Antimutagenic and Other Biological Activities: Protoanemonin and anemonin have been associated with antimicrobial, fungicidal, antimutagenic and antipyretic activities in the literature concerning *Ranunculus* species¹⁸.

However, the biological activity of an isolated compound should not automatically be attributed to the whole plant. Differences in extraction method, concentration, plant part, chemical stability and metabolism can produce markedly different pharmacological outcomes.

Enzyme Inhibition: Enzyme inhibition potential of various fractions of *Ranunculus sceleratus* have been checked against α -glucosidase, butyryl cholinesterase, acetyl cholinesterase and lipoxygenase enzymes. n-Butanol fraction showed very good activity ($77.5 \pm 1.0\%$ inhibition at 0.1 mg/mL) against α -glucosidase¹⁵.

CONCLUSION: *Ranunculus sceleratus* L. is a pharmacologically interesting medicinal plant with a long history of traditional use and a chemically diverse phytochemical profile. Experimental investigations provide evidence for anti-inflammatory, antimicrobial, antifungal, antihypertensive and hepatobiliary activities. Anti-inflammatory research is particularly notable because both crude extracts and isolated

constituents have demonstrated activity in experimental systems. Recent chemical studies have expanded the known metabolite profile of the species and identified new benzopyran derivatives capable of suppressing inflammatory mediators in macrophage cells.

At the same time, *R. sceleratus* cannot be considered a clinically established medicinal agent. Most available evidence remains preclinical, and there is a significant lack of standardized extracts, pharmacokinetic information and controlled human trials. Furthermore, the presence of ranunculin-derived protoanemonin makes toxicity a major consideration, particularly with fresh plant material².

Overall, *R. sceleratus* represents a promising source of biologically active natural products, but its future pharmaceutical development requires a balanced approach integrating phytochemical standardization, mechanism-based pharmacology, toxicological assessment and clinical validation.

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CONFLICT OF INTEREST: Nil

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