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Review Article

Ranunculaceae as a Reservoir of Bioactive Phytochemicals: Ethnopharmacological Insights, Mechanistic Perspectives, and Drug Discovery Potential

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ABSTRACT

The scientific need to develop bioactive molecules from plants as sources of mechanistically novel therapeutics has been sparked by the alarming phenomenon of antimicrobial resistance, the therapeutic limitations of the current pipeline of nonsteroidal anti-inflammatory drugs and the lack of innovation in the development of antibiotics. The Ranunculaceae is one of the most pharmacologically promising, but underutilized groups in the plant kingdom, with some 2500 species belonging to 59 genera found throughout temperate regions of the world. This review combines the family's botanical and taxonomic organization (into five subfamilies, the boundaries of which are predicted for the chemistry by pharmacophylogenetic analysis) with a systematic description of its four major classes of secondary metabolites: triterpenoid saponins, diterpene alkaloids, benzylisoquinoline alkaloids, and the lactone anemonin derived from the ranunculin. The traditional use in Traditional Chinese Medicine, Ayurveda, Unani and African traditional medicine is critically analyzed based on the extent of pharmacological validation. Mechanistic evidence shows that oleanane saponins, berberine, and anemonin act synergistically to modulate the TLR4/NF-κB axis, induce the Keap1-Nrf2-HO-1 antioxidant pathway, and have structurally different mechanisms of action which damage microbial membranes. Preclinical structure-activity relationship studies show that the anti-inflammatory and cytotoxic potency is mainly dependent on the monodesmosidic structure configuration and aglycone identity. The mechanisms of translational barriers such as poor oral bioavailability, haemolytic liability of saponins, and narrow therapeutic window of aconitine are discussed and some strategies which can be used to overcome these barriers by encapsulating drugs in nanoparticles and by computational drug discovery are reviewed. The clinical course of berberine in metabolic disease is a proof of concept for the drug development potential

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of the family.

INTRODUCTION

A huge scientific interest in plant-derived bioactive molecules as sources of structurally novel drug candidates is now resurfacing due to the convergence of three major therapeutic challenges, namely the rising prevalence of oxidative stress associated with chronic diseases, the lack of long-term anti-inflammatory pharmacotherapy and the ever-increasing global crisis of antimicrobial resistance [1]. In 2019, there were estimated to be 1,270,000 deaths due directly to antimicrobial resistance related to a bacterial infection, and 4,950,000 deaths due to resistant pathogens in total. These numbers have increased since 2019 and are expected to double by 2050 if effective measures are not implemented to address the crisis [2]. These figures are higher than the number of people who die every year from TB, malaria and HIV/AIDS combined and there are very few drug candidates in the antibiotic development pipeline with novel mechanisms of action [3]. At the same time, the drugs that form the cornerstone of the treatment of pain and inflammatory disease (conventional NSAIDs) have well documented side effects such as gastroulceration and bleeding due to the suppression of the gastroprotective prostaglandins, and the development of selective COX-2 inhibitors as a gastroprotective alternative to conventional NSAIDs was followed by a heightened awareness of the increased cardiovascular risk associated with these products (myocardial infarction and stroke) [4]. Despite incremental molecular modifications of the existing structures, these clinical drawbacks have not been addressed and the urgent need for multi-target anti-inflammatory and antimicrobial drugs with a good safety profile in humans has never been greater [5].

In this context, it is important to note that the plant kingdom, and particularly the family Ranunculaceae, represents one of the most scientifically plausible and historically documented sources of bioactive secondary metabolites that could be systematically moved into the translational development [6]. The buttercup or crowfoot family, Ranunculaceae, includes about 2500 species, in about 59–60 genera, the greatest number of species being found in the temperate and cold regions of the Northern Hemisphere. These genera are represented by a vast array of species, the numerically dominant being Ranunculus (ca. 600 spp.), Delphinium (ca. 365 spp.), Thalictrum (ca. 330 spp.), Clematis (ca. 325 spp.) and Aconitum (ca. 300 spp.), all of which constitute an extraordinary reservoir of both chemical and morphological diversity [7]. The use of several of these genera in traditional medicine goes back many thousands of years: Coptis chinensis for the production of berberine in Traditional Chinese Medicine (TCM); Aconitum species as a source of analgesics and anti-inflammatory in Ayurvedic and TCM preparations and various Clematis and Ranunculus spices as wound healing and anti-inflammatory agents in African and European traditional medicine that have been investigated pharmacologically in part only and whose activity mechanisms are still not fully understood [8].

The Ranunculaceae is unique in plant families studied for their medicinal properties for the unusually close relationship between the plant families and its chemistry. By comparing the chemical constituent profiles with the evolutionary relationships between the taxa, the concept of pharmacophylogeny suggests that the chemical classes cluster predictably within subfamilies and tribes of the Ranunculaceae and therefore allows the prediction of the likely chemical composition of under-studied taxa from their phylogenetic

relationship to characterized species. This principle is of great practical importance in the rational design of new drugs; it allows species to be targeted for investigation, rather than being screened one by one [9].

This review summarizes the current knowledge on the Ranunculaceae as a pharmacological resource, encompassing their botanical and taxonomic structure, their diversity in secondary metabolites belonging to various chemical classes, the ethnopharmacological values in multiple traditional medicine systems, their mechanistic pharmacological evidence from anti-inflammatory, antioxidant and antimicrobial pathways, the available preclinical evidence base and the challenges and new strategies that pave the way towards clinical applications. Table 1 summarizes the taxonomic and ethnomedicinal coverage of the most therapeutically significant genera of the family. This review is designed to go beyond simply describing the catalogue and provide a critically organized framework highlighting areas of strength, weaknesses, and opportunities for investments that are scientifically sound to produce developable drug candidates from this remarkable chemical heritage of field.

BOTANICAL AND TAXONOMIC ARCHITECTURE OF THE RANUNCULACEAE

The Ranunculaceae is one of the earliest-diverging families with respect to the eudicots in both chromosome-based and morphological classifications, and in molecular phylogenetic studies. Within the modern literature, the family is split into five subfamilies: Ranunculoideae, Thalictroideae, Coptidoideae, Hydrastidoideae, and Glaucidioideae, the boundaries of which were improved by the incorporation of molecular data, in addition to cytological and chemotaxonomic markers. The largest is Ranunculoideae with about 81% of the species in the 10 recognised tribes, among which are Anemoneae, Delphinieae, Cimicifugeae, Helleboreae, Ranunculeae and Nigelleae. The Thalictroideae contain about 450 species (such as Thalictrum and Aquilegia) and the Coptidoideae contain about 17 species (such as Coptis and its relatives). The following sections are monotypic: Hydrastidoideae, with Hydrastis canadensis; and Glaucidioideae, with Glaucidium palmatum [10,11].

This subfamiliar structure has a much broader pharmacologic importance than taxonomy. A correlation between secondary metabolites, pharmacology and the phylogeny has been determined by a methodology called pharmacophylogenetic analysis, and a clear correlation has been found between certain subfamilial and tribal groups and the presence of certain classes of secondary metabolites [12]. The Coptidoideae and some genera in Thalictroideae are rich in benzylisoquinoline alkaloids (including berberine and magnoflorine); the tribe Delphinieae (genera Aconitum and Delphinium) is characterized by diterpene alkaloids such as aconitine and its congeners; triterpenoid saponins predominate in the genera of Anemoneae (Clematis, Anemone and Pulsatilla); and ranunculin, a biosynthetic precursor of the reactive lactone protoanemonin, is widely distributed in Ranunculeae and some of the related tribes. Critically, co-occurrence of both ranunculin and magnoflorine in some genera suggests that subfamily boundaries do not provide absolute chemical partitions and instead provide probabilistic chemical tendencies, which could be used to rationalise the prioritisation of species that have yet to be studied for their chemistry [13].

Within this family, there is also morphological diversity that is also significant, relevant to the production of secondary metabolites. The

Ranunculaceae is dominated by the herbaceous annuals and perennials, but Clematis forms the major lianescent lineage with the majority of species being vigorous, woody, climbing vines and lianas found mostly in the temperate parts of the Northern Hemisphere; the number of species recorded varies from 325 to 370, depending on the taxonomic authority consulted [14]. Clematis have a woody climbing growth form, which implies that they are under different herbivory, mechanical, and light-competition pressures when compared with herbaceous relatives, and in general, a strategy of chemical defence is thought to favour the production of triterpenoidal saponins and flavonoids in tissues of stem, root, and leaf. The following sections exploit this growth form–chemistry relationship throughout the family as a rational means of navigating the chemical terrain of the family, by which we mean to explain why certain genera have been found to be more prolific than others in the production of medicinally active compounds [14].

Table 1: Taxonomic Classification and Ethnomedicinal Applications of Therapeutically Significant Genera within the Ranunculaceae Family [15–17]

Genus	Subfamily / Tribe	Species count (approx.)	Geographic distribution	Traditional medicine system	Principal ailments treated
Clematis	Ranunculoideae / Anemoneae	~325–370	Temperate Asia, Europe, N. America	TCM, Ayurveda, African ethnomedicine	Rheumatism, bone disorders, gout, wound healing, infections, leprosy
Aconitum	Ranunculoideae / Delphinieae	~300–343	Himalayas, alpine Asia, Europe	Ayurveda, TCM	Pain, rheumatic fever, inflammation, cardiovascular disease, tumours
Ranunculus	Ranunculoideae / Ranunculeae	~600	Worldwide (all continents)	European herbal, African, Unani	Jaundice, malaria, rheumatism, asthma, gout, skin disorders
Anemone	Ranunculoideae / Anemoneae	~150	Temperate Northern & Southern hemispheres	TCM, European herbal	Cancer, inflammation, antimicrobial, menstrual disorders
Pulsatilla	Ranunculoideae / Anemoneae	~33	Europe, Asia, N. America	TCM, European herbal	Menstrual disorders, dysentery, bacterial infections, inflammation
Thalictrum	Thalictroideae	~330	Asia, Europe, N. America	Ayurveda, TCM, Unani	Hepatic disorders, fevers, dermatological conditions, antimicrobial
Coptis	Coptidoideae	~17	SW China, India, N. America	TCM, Ayurveda	Gastrointestinal infections, dysentery, metabolic disease, diabetes
Delphinium	Ranunculoideae / Delphinieae	~365	N. Hemisphere	Unani, Ayurveda, African	Neuralgia, pain, parasitic infections, insecticidal use
Aquilegia	Thalictroideae	~70	Europe, N. America, Asia	European herbal	Liver disease, skin disorders, diuretic

Nigella	Ranunculoideae / Nigelleae	~20	Mediterranean, W. Asia	Unani, Ayurveda, Middle Eastern	Respiratory infections, diabetes, antimicrobial, antioxidant

SECONDARY METABOLITE DIVERSITY-CHEMICAL CLASSES AND STRUCTURAL SIGNIFICANCE

The pharmaceutical significance of the Ranunculaceae is based on the fact that this plant family contains at least four distinct classes of secondary metabolites with highly different chemical structures that are responsible for the biological activity and the taxonomic group to which each is predominantly found. It is important to have a systematic knowledge of these compound classes before meaningful inferences can be drawn from mechanistic pharmacology (as summarized in Table 2): Triterpenoid saponins, diterpene alkaloids, benzylisoquinoline alkaloids, ranunculin and its downstream lactones, and a broad layer of flavonoids and polyphenols [18].

Triterpenoid saponins are the predominant and most well characterised metabolite class of the medically important genera of the Ranunculoideae, especially in the tribe Anemoneae. In Clematis, oleanolic acid and hederagenin are the pentacyclic oleanane aglycones which are the main component of the triterpenoid saponins with sugar chains, consisting of glucose, rhamnose, galactose, arabinose, xylose and ribose residues, arranged in different sequences. Clematis contains more than 120 saponins, of which about 70 are oleanolic acid type, about 50 are hederagenin type, and two are gypsogenin type; all of the aglycones are oleanane pentacyclic triterpenoids [19]. Saponins containing oleanolic acid and hederagenin are also major bioactive constituents in Pulsatilla species and 9 triterpenoid saponins including some novel compounds have been isolated from Pulsatilla chinensis roots, which have shown to be cytotoxic towards human leukaemia cells (HL-60). In the case of anti-tumour activity, the bioactivity of these saponins is closely linked to the structural features: monodesmosidic saponins with a free carboxyl at position C-28 of the hederagenin aglycone, were found to be more potently cytotoxic and anti-tumour active than the corresponding bisdesmosidic counterparts, in which both C-3 and C-28 positions are glycosylated, a principle which also applies to anti-inflammatory and antimicrobial activities [20].

Aconite and Delphinium are characterized by diterpene alkaloids that form the chemotaxonomic signature of the tribe Delphinieae. The C19-diterpenoid (10,11-seco) alkaloid most prevalent in Aconitum species is aconitine, a cardiotoxic and neurotoxic compound which contains an acetyl group at C-8 and a benzoyl ester at C-14, both of which are mainly responsible for its toxic effects by interacting with voltage-gated sodium channels. Although this structural arrangement gives this compound a very narrow therapeutic window, this compound also shows anti-inflammatory, analgesic, and antitumour properties in carefully controlled experimental studies [21]. The pharmacological duality is due to the fact that the same ester substituents that activate the sodium channels at toxic concentrations also produce partial agonism at sub-toxic concentrations, which results in modulation of ion flux. This chemistry underlies the methods of preparing TCM, with the extended boiling (4–6 hours) or steaming (6–8 hours) time

used to sequentially break down the diester aconitine to the less toxic monoester benzoylaconine and finally to the non-toxic aconine, thereby demonstrating that processing can be used to modify the structure and unlock therapeutic benefits while reducing toxicity [22].

Benzylisoquinoline alkaloids form the most abundant class of alkaloids in the Coptidoideae and berberine, palmatine, coptisine, and epiberberine are found mainly in the rhizomes of the Coptis species. The antimicrobial and cytotoxic properties of Berberine are attributed mainly to its planar ring system that allows intercalation with DNA and inhibition of topoisomerase II, which contains a quaternary isoquinoline skeleton. In addition to such effects, the inhibition of α-glucosidase and modulation of AMPK-dependent metabolic pathways has led berberine to be the most clinically advanced alkaloid from any genus of the Ranunculaceae, having been shown to be active in type 2 diabetes and metabolic syndrome. Some genera of Thalictroideae, such as Thalictrum, contain benzylisoquinoline alkaloids such as magnoflorine and thalictrine, and the occurrence of magnoflorine and ranunculin in some genera bridges the subfamily boundaries [23].

Ranunculin is a glucoside with the molecular formula $C_{11}H_{16}O_8$ that functions as the biosynthetic precursor to the reactive lactone protoanemonin across numerous Ranunculaceae species. Damage to the plant tissue causes the enzyme β-glucosidase to convert ranunculin to its aglycone, then the protoanemonin is created spontaneously by the loss of water [24]. Due to the inherent chemical instability of protoanemonin, it readily cyclodimerizes to anemonin, which is the best form for pharmacological characterisation. Anemonin has anti-inflammatory, anti-infective and antioxidant properties and has demonstrated the most promise of the three in the treatment of experimental models of arthritis, cerebral ischaemia, and ulcerative colitis, in part due to its ability to inhibit nitric oxide (NO) synthesis and to reverse lipopolysaccharide (LPS) induced inflammation [25].

The flavonoids and polyphenols constitute a chemically varied layer that is widely spread throughout the family. Kaempferol, quercetin and apigenin glycosides have been detected in species of Ranunculus and some of the compounds have been characterised, such as kaempferol 3-O-rutinoside (nicotiflorin), vitexin and orientin. Besides saponins, Clematis species also contain flavonoid glycosides (flavonoids, lignans, steroids, polyphenols and coumarins) which are extracted in different proportions depending on the solvent polarity, with ethanol and methanol favourably yielding flavonoid aglycones and mono-glycosides, and aqueous solvents favourably yielding polar glycosides and saponins. This extraction-dependent variation in composition has been cited as a major reason for the discrepancies in the reported pharmacological activities reported in various studies where solvent systems vary but the plant material is the same; a methodological point of relevance to the process of quality standardisation of drug production [26].

Table 2: Major Bioactive Phytochemical Classes of Ranunculaceae: Representative Compounds, Source Genera, Structural Scaffolds and Reported Pharmacological Activities [27–29]**.**

Chemical class	Representative compound	Source genus/species	Structural scaffold	Key pharmacological activities
Triterpenoid saponin (oleanolic type)	Clemchinenoside A	*Clematis chinensis*	Oleanolic acid aglycone + oligosaccharide chain at C-3	Anti-inflammatory, antimicrobial, cytotoxic

Triterpenoid saponin (hederagenin type)	Cussonside B	*Clematis argentilucida*	Hederagenin aglycone + arabinosyl-rhamnosyl chain at C-3	Cytotoxic (HL-60, Hep-G2), anti-inflammatory
Triterpenoid saponin	Pulsatilla saponin D	*Pulsatilla chinensis*	Oleanolic acid, bisdesmosidic	Anticancer, antitumour (leukaemia cell lines)
Triterpenoid saponin (gypsogenin type)	Gypsogenin saponin	*Pulsatilla cernua*	Gypsogenin aglycone; first reported from genus	Neuroprotective ($A\beta_{25–35}$ cytotoxicity model)
Diterpene alkaloid	Aconitine	*Aconitum carmichaelii*	C19-diterpenoid; acetyl at C-8, benzoyl ester at C-14	Analgesic, anti-inflammatory, cardiotoxic/cardioactive, antitumour
Diterpene alkaloid	Hypaconitine	*Aconitum kusnezoffii*	C19-diterpenoid with methyl ester replacing acetyl at C-8	Analgesic, antitumour, lower cardiotoxicity than aconitine
Benzylisoquinoline alkaloid	Berberine	*Coptis chinensis*	Quaternary isoquinoline with methylenedioxy ring	Antimicrobial, antidiabetic, anti-inflammatory, cytotoxic
Benzylisoquinoline alkaloid	Magnoflorine	*Thalictrum* spp., *Clematis* spp.	Aporphine-type isoquinoline	Antimicrobial, antifungal, antispasmodic
Ranunculin / lactone	Anemonin	*Ranunculus*, *Anemone*, *Pulsatilla*	Cyclodimerised lactone from protoanemonin	Anti-inflammatory (NO inhibition), anti-infective, antioxidant
Flavonoid glycoside	Nicotiflorin (kaempferol 3-O-rutinoside)	*Ranunculus sceleratus*	Kaempferol aglycone + rutinosyl at C-3	Antioxidant, anti-inflammatory, cardioprotective
Flavone C-glycoside	Vitexin (apigenin 8-C-glucoside)	*Ranunculus* spp.	Apigenin with C-C linked glucose at C-8	Antioxidant, anti-inflammatory, neuroprotective
Lignan	(+)-Pinoresinol	*Pulsatilla chinensis*	Furofuran lignan skeleton	Cytotoxic (HL-60 cells), antioxidant
Coumarin	Isoscopoletin	*Ranunculus sceleratus*	7-Hydroxy-8-methoxycoumarin	Antifungal, smooth muscle relaxant

ETHNOPHARMACOLOGICAL HERITAGE AND TRADITIONAL USE SYSTEMS

The ethnopharmacological history of the Ranunculaceae is among the geographically broadest and time deepest of any plant family, with more than two millennia of documented use throughout Asia, Europe, the Middle East and sub-Saharan Africa. This use is not haphazard, however, but is highly representative, so that the genera most commonly used in each tradition are those most abundant in the species and most broadly distributed in the ecology in that tradition [30].

The Ranunculaceae belongs to the most basic of the traditional Chinese medicine, and there are several entries in the pharmacopoeia. Wei Ling

Xian is made from the roots and rhizomes of *Clematis chinensis, C. hexapetala* and *C. mandshurica*, used to dispel wind-dampness, unblock channels and relieve pain, thus corresponding to inflammatory musculoskeletal conditions such as rheumatoid arthritis, gout and spondylitis. The chuan mu tong is a diuretic and channel clearing agent from the *C. armandii* and *C. montana*. *Coptis chinensis* (Huang Lian) is a classic Chinese medicinal herb that has been recorded for more than 2000 years in various herbal medicines for gastrointestinal infection, dysentery and metabolic heat, especially its rhizome containing berberine, which was first mentioned in the *Shennong Bencao* Jing [31]. Among the most highly regarded and manipulated TCM agents for centuries have been the Aconitum species (Fu Zi, Chuan Wu) whose native aconitine content is removed before use in formulating for cold-induced pain, cardiac insufficiency and rheumatic disease. One of the most striking examples of the empirical ethnopharmacology predictions of the chemical basis of aconitine hydrolysis was the fact that the TCM practitioners independently arrived at the same conclusion: thermal processing as a toxicity reduction strategy [32].

Aconitum heterophyllum (Ativisha) and Aconitum ferox are used mainly for the treatment of fever and pain, and as nerve tonics, especially in Ayurvedic and Unani medicine; the Ayurvedic purification process called Shodhana is similar to the TCM process of boiling and has a similar functional role of detoxification by modification of the hydrolytic alkaloid. *Thalictrum foliolosum* (also containing berberine), spread over the hills of the Himalayan range from Shimla to Sikkim, is used in Ayurvedic medicine to treat hepatic and digestive ailments, especially as an alternative for *Coptis teeta. Nigella sativa*, which belongs to the tribe Nigelleae in Ranunculoideae, has been used in Unani, Ayurvedic, Arab and Malay medicine for treating respiratory infections, metabolic disorders and hypertension, and the key compound in the seed oil fraction is thymoquinone, which makes up 30-48% of the product and is responsible for the majority of the pharmacological effects described [33].

Clematis brachiata (traveller's joy) is used in African ethnomedicine for wound healing, antimicrobial use and anti-inflammatory conditions; experimental validation reveals that aerial extract inhibited the carrageenan-induced paw oedema at doses of 100–400 mg/kg with a 400 mg/kg dose comparable to indomethacin. Most of the plants used in the European herbal tradition are derived from Ranunculus and *Clematis vitalba* (old man's beard) as topical vesicants and counter-irritants, and they contain ranunculin which is converted to protoanemonin on damage [34].

The uniformity of therapeutic indication of the systems surveyed is an epistemic bonus that strengthens the ethnopharmacological record: the convergence of therapeutic indications for preparations of Clematis in Han Chinese medicine and in the practice of Southern Africa, provides an important prior probability to guide the current research into the mechanism of action. However, several claim types are still poorly validated by mechanistic or clinical pharmacology, and are just as clearly defined gaps of research, where ethnobotanical signal strength is high, but scientific translations have not yet happened, such as claims of hepatoprotective activity for Thalictrum species, and antimalarial activity for Ranunculus species in Africa [35].

MECHANISTIC PHARMACOLOGY-ANTI-INFLAMMATORY, ANTIOXIDANT AND ANTIMICROBIAL PATHWAYS

Pharmacology of phytochemicals from the Ranunculaceae plant family involves three interconnected biological domains, inflammation, oxidative stress, and microbial virulence, each of which is biochemically interconnected, such that reactive oxygen species (ROS) generated at sites of infection act to further stimulate inflammatory cascades, and chronic inflammation further increases cellular oxidative burden leading to microbial virulence. A knowledge of these family-derived phytochemicals' molecular targets and how these domains are modulated is key in order to identify these as viable multi-target therapies.

Anti-inflammatory mechanisms- Modulation of the NF-κB signalling axis is the most mechanistically documented anti-inflammatory mechanism of phytochemicals of the Ranunculaceae family. LPS-induced RAW264.7 macrophage cells showed that the extract of Clematis mandshurica root (CRE) inhibited the production of tumor necrosis factor (TNF) alpha, interleukin (IL) 1 beta, IL-6, nitric oxide (NO) and prostaglandin E2 (PGE2), which led to a corresponding reduction in the mRNA and protein expression of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), and nuclear factor (NF)-kappaB, and inhibition of MAPK phosphorylation. The two saponins, clematomandshurica saponins A and B, isolated from the same species, exhibited direct inhibitory activity against COX-2 with IC_{50} values of 2.66 μM and 2.58 μM respectively, which are comparable to a great number of synthetic COX-2 inhibitors, although further interpretation of these values requires the use of the selectivity data provided for the various COX isoforms [36]. The anti-inflammatory activity of AR-6, a triterpene saponin isolated from Clematis chinensis, in rats with adjuvant-induced arthritis was found to be dose dependent, lowered the serum levels of PGE2, TNF-α and nitric oxide, and prevented synovial membrane hyperplasia; these anti-inflammatory effects were correlated with suppression of NF-κB, TNF-α and COX-2 in a collagen-induced arthritis model. The pentacyclic triterpenoid aglycone shared by many Clematis and Pulsatilla saponins, hederagenin, suppressed ROS accumulation and extracellular matrix degradation by downregulating MMPs and ADAMTS5, and downregulated the JAK2/STAT3/MAPK signalling pathway in chondrocytes, partially inhibiting the pathway to exert its chondroprotective activity. The multitarget anti-inflammatory properties of oleanane triterpenoid scaffold, which is the structural backbone shared by the major metabolites of Clematis and Pulsatilla, are not limited to a single pathway, but rather have a genuine multi-target anti-inflammatory pharmacology across the various experimental systems examined [37].

In addition to the saponin class, anti-inflammatory properties of anemonin are exerted through other mechanisms such as inhibiting nitric oxide (NO) synthesis and directly suppressing LPS-induced inflammatory responses, with demonstrated efficacy in experimental models of ulcerative colitis and cerebral ischaemia. The mutual complementarity of the lactone (anemonin) and saponin fractions within a single plant extract offers a scientific rationale for the enhanced/increased anti-inflammatory activity of whole plant extracts relative to isolated fractions that are standardised to a single compound class, which is relevant for standardisation of Ranunculaceae preparations for pharmacological testing [38].

Antioxidant mechanisms- Antioxidant activity of phytochemicals of Ranunculaceae plants is either enzymatic or non-enzymatic and structurally different classes of compounds act through

structurally different molecular pathways. The principal alkaloid of Coptis, berberine, is the most pharmacologically developed compound in the Ranunculaceae that can activate the Keap1–Nrf2–HO-1 axis, which results in the nuclear translocation of Nrf2 and upregulation of the transcription of antioxidant response element (ARE)–driven genes encoding superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). Berberine also activates the AMPK pathway to decrease the generation of mitochondrial ROS, and can directly scavenge free radicals via its hydroxyl and methoxy groups that can donate electrons or hydrogen atoms to free radicals and form coordination bonds with iron and copper ions, which inhibit metal-catalysed Fenton chemistry. The antioxidant activity of flavonoids, which is mostly attributed to their hydrogen-donating ability, is achieved by phenolic hydroxyl groups in the B-ring and at the 3-position of the flavonol scaffold, and is strongly dependent on the number and position of the hydroxyl groups, with the former playing the major role in the DPPH and ABTS assays. Thymoquinone of Nigella sativa also regulates the Nrf2 pathway apart from its direct radical scavenging action and its antioxidant activity is thought to be the key mechanistic pathway for the hepatoprotective and nephroprotective effects ascribed to this genus in Unani and Ayurvedic medicine [39].

Antimicrobial mechanisms- Antimicrobial pharmacology of the family acts by at least three different mechanisms, which have been characterized to varying extents of resolution. The amphipathic properties of saponins (hydrophobic sapogenin moiety and hydrophilic sugar chains) allow them to disrupt bacterial membranes, causing curvature stress, increased membrane permeability, loss of proton motive force, leakage of the internal bacterial content, and death. Due to the absence of cholesterol in the membranes of bacteria, classical saponin pore-formation mechanism cannot explain saponin activity on bacteria, and the mechanism of pore-formation on bacteria is attributed to changes in membrane fluidity and integrity by sterol-cholesterol interaction. This mechistic difference has a therapeutic relevance because it suggests that there is some degree of selectivity that may be utilised for therapeutic purpose. In addition to membrane disruption, saponins have been demonstrated to inhibit the ability of biofilm communities to form by lowering surface tension and weakening the structural integrity of their extracellular polymeric substance (EPS) matrix, thereby disrupting the communities directly.In addition to membrane disruption, saponins have been demonstrated to inhibit the ability of biofilm communities to form by lowering the surface tension and by weakening the structural integrity of the biofilm's extracellular polymeric substance (EPS) matrix, thereby disrupting the communities directly, which is especially relevant to management of chronic infections in the era of resistance. In addition to these membrane level effects, Berberine has antimicrobial activity that acts through a different mechanism: its planar tetracyclic isoquinoline structure intercalates with bacterial DNA, blocking topoisomerase activity and disturbing chromosome segregation, and there is evidence that berberine inhibits the multidrug efflux pumps in some gram-positive species, re-sensitizing them to antibiotics that are normally pumped out. It is the multi-target antimicrobial pharmacology of the Ranunculaceae (membrane disruption (saponins), DNA/topoisomerase targeting (berberine) and reactive lactone alkylation of sulfhydryl groups (protoanemonin)) that is not yet matched by any combination of synthetic antimicrobial classes [40,41].

PRECLINICAL EVIDENCE AND STRUCTURE–ACTIVITY RELATIONSHIPS

There is a large amount of preclinical evidence available for the Ranunculaceae, including in vitro cell-based assays, and in vivo animal models, but the quality and interpretive value of the studies vary widely in the literature. If analyzed critically, several conclusions become apparent that go beyond the level of generalized activity descriptions and start to develop the type of structure–activity relationships (SAR) and dose–response characterizations needed for drug discovery.[42]

The anti-inflammatory pharmacology of Clematis saponins in adjuvant- and collagen-induced arthritis models is one of the most consistently validated experimental findings, with a fairly well understood mechanism of action. Oral treatment with AR-6 of rats with AIA resulted in dose-dependent reduction of clinical symptom severity and significant decreases in plasma PGE2, TNF-α and nitric oxide in the animals. Specifically, the subcutaneous administration of *C. mandshurica* extract in the arthritic rats resulted in a decrease in paw swelling that was similar to dexamethasone treatment, and a marked decrease in the production of TNF-α and IL-1β with an increase in the anti-inflammatory cytokine IL-10. The closest for the entire family is a rheumatoid arthritis patient clinical trial where *C. mandshurica* capsules showed therapeutic efficacy similar to celecoxib which did not produce significant adverse effects in a randomized, double-blind evaluation [43].

The antioxidant evidence is broad but the quality of the methods is limited, typical of pharmacology studies of plants. The best in vitro study conducted to date was the evaluation of 19 extracts (from 16 species of Ranunculaceae) using the ORAC and DPPH assays, with the extract from Aconitum toxicum showing the strongest DPPH radical-scavenging activity (IC_{50} of 18.7 µg/mL) and ORAC activity (IC_{50} 92.6 µg/mL). Thalictrum minus extract inhibited COX-2 (IC_{50} 49.68 µg/mL), 5-LOX (IC_{50} 76.47 µg/mL), but not COX-1 (IC_{50} greater than 128 µg/mL), which is comparable to the selectivity profile of the selective COX-2 inhibitors, but with a crude extract instead of a purified compound. In the same study, Helleborus purpurascens root extract exhibited the highest inhibitory activity against COX-1, COX-2 and 5-LOX with IC_{50} values of 5.64, 10.33 and 3.84 µg/mL respectively and GC-MS analysis revealed some of the activity was due to α-linolenic acid in the bioactive fraction. The fatty acid fractions downregulated IL-6 and COX-2 expression in cell-based models, suggesting that the bioactive activity of this species is not solely due to the presence of the ranunculins/anemonins chemistry, but may also involve lipid-derived mediators .

Pulsatilla species have especially concrete antimicrobial evidence and mechanism. Pulsatilla saponins have been consistently shown to exhibit antimicrobial and anti-inflammatory activity in various experimental systems and comprise primarily anemoside B4 (pulchinenoside C), pulsatilla saponin D (SB365), and pulchinenoside A. P. chinensis saponins also decreased inflammatory markers in DSS-induced ulcerative colitis rats, indirectly by probably normalizing intestinal flora, besides the direct antibacterial effect reported in previous studies. The extract of Anemone transsilvanica exerted selective antiproliferative activity against Caco-2 colorectal cells, at a concentration of 46.9 µg/mL and 70.2 µg/mL against HT29 cells, respectively, with low toxicity against the normal intestinal cells FHs74Int. The extract of Aconitum vulparia exerted high antiproliferative activity against Leishmania infantum promastigotes and

amastigotes, with an IC_{50} of 18.8 µg/mL and 29.0 µg/mL, respectively, and low toxicity against the normal intestinal cells FHs74Int [44].

The SAR data from the literature of the Ranunculaceae saponins are of pharmacological interest. The study of oleanane triterpenoid derivatives of Pulsatilla saponins revealed that C-28 oligosaccharide chain is essential to anti-UC activity, and the C-23 methyl group plays a role in anti-UC action, whereas C-28-COOH is responsible for haemolytic toxicity; this has direct implications in the design of semi-synthetic derivatives that could retain anti-inflammatory potency while avoiding the haemolytic liability by esterification and amide formation at C-28. An interesting observation is that the monodesmosidic counterparts with free C-28 carboxyl group are more anti-inflammatory and cytotoxic compared to the bisdesmosidic counterparts, with higher haemolytic risk as well, which corroborates the idea that the key medicinal chemistry problem is the optimisation of the sugar chain arrangement for this series of compounds. The disadvantage of this preclinical research is that most of the antimicrobial and antioxidant research performed so far are on crude extracts and do not identify what compounds are responsible for them, thus making the SAR analysis difficult and making it not reliable to compare different studies [45].

Table 3. Summary of Preclinical Pharmacological Studies on Selected Ranunculaceae Species: Models, Endpoints, Active Fractions, and Outcome Metrics [46,47]

Species	Plant part/ Extract	Compound/ Fraction tested	Experimental model	Pharma-cological endpoint	Key finding	Activity type
Clematis chinensis	Root	Triterpene saponin AR-6	Adjuvant arthritis in rats (in vivo)	PGE2, TNF-α, NO; synovial histology	Dose-dependent reduction in inflammation markers; abolished synovial hyperplasia	Anti-inflammatory
Clematis mandshurica	Root	Crude root extract (CRE)	LPS-stimulated RAW264.7 macrophages (in vitro); carrageenan paw oedema (in vivo)	TNF-α, IL-1β, IL-6, iNOS, COX-2, NF-κB	Significant down-regulation of all inflammatory markers; paw oedema reduction comparable to dexamethasone	Anti-inflammatory
Clematis mandshurica	Root	Clematomand-shurica saponins A & B	COX-2 enzyme inhibition assay	COX-2 IC_{50}	IC_{50} = 2.66 and 2.58 µM respectively (direct COX-2 inhibition)	Anti-inflammatory
Clematis brachiata	Aerial parts	Ethanol extract	Carrageenan paw oedema in rats (in vivo)	Paw volume, body temperature	400 mg/kg dose reduced oedema and fever comparably to indomethacin	Anti-inflammatory/ antipyretic

Aconitum toxicum	Whole plant	Ethanolic extract	DPPH radical scavenging; ORAC assay (in vitro)	IC_{50} (DPPH 92.6 µg/mL; ORAC 18.7 µg/mL)	Highest antioxidant activity among 16 Ranunculaceae species tested	Antioxidant
Helleborus purpurascens	Root	Ethanol extract; FA subfraction	COX-1, COX-2, 5-LOX inhibition (in vitro)	IC_{50} (COX-1: 5.64; COX-2: 10.33; 5-LOX: 3.84 µg/mL)	Most potent multi-enzyme anti-inflammatory of 25 Ranunculaceae species tested; α-linolenic acid identified as contributor	Anti-inflammatory
Thalictrum minus	Root	Ethanol extract	COX-1, COX-2, 5-LOX inhibition (in vitro)	IC_{50} (COX-2: 49.68; 5-LOX: 76.47 µg/mL; COX-1: >128 µg/mL)	Selective COX-2 and 5-LOX inhibition without COX-1 suppression	Anti-inflammatory
Pulsatilla chinensis	Root	Total saponins (PRS; anemoside B4)	DSS-induced ulcerative colitis rat model (in vivo)	Colon histology, inflammatory cytokines, gut microbiome 16S rRNA	Reduced IL-6, IL-1β; improved mucosal barrier; normalised gut flora diversity	Anti-inflammatory/ antimicrobial
Anemone transsilvanica	Whole plant	Ethanolic extract	MTT assay: Caco-2 and HT29 cells (in vitro)	IC_{50} antiproliferative	IC_{50} = 46.9 µg/mL (Caco-2); 70.2 µg/mL (HT29)	Anti-proliferative
Aconitum vulparia	Whole plant	Ethanolic extract	*Leishmania infantum* promastigotes and intracellular amastigotes (in vitro)	IC_{50} parasiticidal	Promastigotes IC_{50} 18.8 µg/mL; amastigotes 29.0 µg/mL; low normal cell toxicity	Antiparasitic/ antimicrobial
Ranunculus Constantino-politanus	Aerial parts	Methanol extract; fatty acid subfraction	LPS-induced IL-6 and COX-2 in SCp2 and Mode-K cells (in vitro)	IL-6, COX-2 expression	Fatty acid fraction (not ranunculin fraction) responsible for IL-6 and COX-2 down-regulation	

TRANSLATIONAL POTENTIAL AND DRUG DISCOVERY PERSPECTIVES

The promise of the Ranunculaceae as therapeutic agents has to be addressed with a combination of challenges that are interrelated and include aspects

of pharmacokinetics, formulation science, toxicology, and regulatory pathway. None of these are small hurdles; several of the family's lead compounds are in a real race with other families of natural products in development at this stage on the basis of their degree of mechanistic validation in preclinical models. Difficulties with bioavailability and delivery. Berberine is the most advanced compound from the Ranunculaceae, and is a prime example of the therapeutic potential and pharmacokinetic problems associated with the family's alkaloids. Oral bioavailability of berberine is low due to its low intestinal absorption, high first pass metabolism, and high efflux as a result of P-glycoprotein [48].

These factors have led to a significant amount of research focus on the design of its delivery system. Nanosuspensions of berberine coated with chitosan have been reported to significantly enhance its oral bioavailability and pharmacological effects in experimental diabetic models, as compared to nanosuspensions of free berberine and metformin (300 mg/kg) in streptozotocin-induced diabetic mice, where the former group resulted in superior hypoglycaemic and lipid normalising effects. For substances that are hydrophilic, but poorly membrane permeable, such as polar Saponin glycosides, phytosome technology represents an alternative, which consists in complexing the phytochemicals with phospholipids, making them compatible with cellular membranes. The unique delivery problem of saponins is their amphiphilic nature and their high molecular weight that generally reduces passive intestinal absorption, coupled with their haemolytic activity at higher systemic concentrations, which sets a limit on the therapeutic window for intravenous formulations; thus, the need for strategies that facilitate targeted intestinal delivery, such as nanoencapsulation, for the targeted delivery of these substances. The main problem with aconitine and related diterpene alkaloids is not bioavailability but rather that the difference between the analgesic/anti-inflammatory dose and the cardiotoxic dose is very small, and nanoparticulate encapsulation in this context is not aimed at increasing bioavailability, but rather to obtain a controlled sustained release to keep plasma levels below the arrhythmogenic limit while maintaining anti-inflammatory levels [49].

As discovery accelerators, in silico tools. The use of network pharmacology and molecular docking on the compounds of the family Ranunculaceae has significantly boosted the understanding of their mechanisms. Network pharmacology analyses of the Pulsatilla decoction (which contains both Coptis chinensis, rich in berberine, and Pulsatilla saponins) revealed that MAPK1, JUN and AKT1 were the core targets, in which quercetin had high binding affinity for all three, illustrating a multi-target mechanism that was consistent with experimental results. Molecular docking studies of compounds isolated from Clematis burgensis against both E. coli DNA gyrase B and human DNA topoisomerase IIα, followed by ADMET prediction using SwissADME and PreADMET, have now started to support the drug-likeness profiling for prioritisation of compounds for follow-on wet-lab work, which is now widely used in natural product lead optimisation. Using network pharmacology in combination with molecular dynamics simulation has become more prevalent to quantify the binding stability and predict off-target interactions, and the contribution of the computer is shifting from hypothesis generation to prioritisation. Research in this computational domain has significantly increased since 2022, as seen in the surge of studies using network pharmacology and molecular docking in herbal medicine research and its increased maturity as a drug discovery tool in

2024. Berberine as proof-of-concept. One of the most instructive leads in the Ranunculaceae is berberine, whose trajectory is the translation. Collectively, its report of clinically meaningful blood glucose reduction in randomised trials, its gut microbiome mediated mechanism (AMPK modulation in intestinal epithelial cells and promotion of beneficial microbial communities), and the expanding literature on nanoformulations reinforces the idea that a compound from this family can be developed from ethnobotany to mechanism to clinical application. The other compounds in the family, and specifically the hederagenin saponins of Clematis and the anemoside B4 from Pulsatilla should be compared to the developmental history of berberine, to see how far the targeted, structured investment of time in pharmacokinetic optimisation and formulation science can go [50].

LIMITATIONS, RESEARCH GAPS, FUTURE PERSPECTIVE

Although the pharmacological literature of the Ranunculaceae is extensive, it has some structural weaknesses which limit its usefulness in translation now. The most significant is the rather patchy nature of phytochemical coverage Clematis, Pulsatilla, Coptis and Aconitum have been investigated in a relatively depth manner, but most of the other 2500 species or so of this family are characterised only by crude extract bioassays, if they are characterised at all. This pharmacophylogenetic architecture of the family is a rational predictive tool for prioritizing under-studied species and this intelligence has not been taken to the task of broadening the chemical coverage beyond TCM prominent genera systematically. At the same time, the antimicrobial and antioxidant literature is overrun with MIC and IC_{50} values of crude extracts which have not been identified with respect to any individual compound, thereby hindering the ability to perform structure–activity analysis and to cite such results in regulatory and/or drug development settings. The lack of clinical trial data for any other compound of any other genus from any other species highlights the enormous research-practice gap that exists at the moment, especially since the first compound was berberine, and no other compound within the Coscinium genus has been studied [51].

The three future directions have the highest scientific payoff. Firstly, metabolomics guided dereplication, combined with multi-omics analysis (transcriptomics, proteomics, metabolomics as applied to Ranunculaceae species (e.g., Pulsatilla species)) would provide a rapid means of identifying novel secondary metabolites and their biosynthetic genes without the limitations of conventional isolation chemistry at the family scale, and now demonstrated to be possible for the characterisation of triterpenoid saponins in the family. Second, AI can be used for virtual screening in the chemical space of the family to systematically select compound–target interactions to be validated by experimentation, thereby using AI to enhance QSAR modelling in the documented chemical space. Third, strategies specifically developed for nanoformulation for oleanane saponins, which take into account their intrinsic amphiphilicity and the necessity to control their haemolytic liability, are the most apparent routes to making the most important group of saponins of the family clinically administrable. These three investments constitute the research programme most likely to make the best use of the exceptional heritage of the Ranunculaceae in a deployable medicine [52].

CONCLUSION

The pharmacology of the Ranunculaceae is scientifically sound and practically impactful, with

evidence across this review pointing to a multi-target, millennia-old ethnomedicinal profile, and a well-defined chemical logic that has been applied to rational compound prioritisation based on evolutionary relationships. But the field has not been able to show the same proportionate clinical results, and the reason for this is just as significant as finding a way to close it. The best answer is that it is not the chemistry of the family that is the limiting factor; the compounds are very active, they have been characterised mechanistically and, in a number of cases, they have been clearly demonstrated to be active in complex in vivo models. The limiting factors are structural: the evidence base for preclinical research is methodological in nature and occurs at the evidence level of the individual compound rather than the level of the compound in its specific chemical class in too many published studies; the pharmacokinetic challenges of the dominant class of saponins have not yet been addressed with the level of systematic delivery science investment they deserve, and the clinical evidence infrastructure beyond berberine is nonexistent. The problems are solvable, and the advances made in addressing them through bioassay-guided isolation of active molecules instead of crude-extract pharmacology or through nanoformulation platforms specifically developed to harbor amphipathic glycosides, and through the use of network pharmacology pipelines which are able to explore the family's chemical space by means of a computational approach, scalable in dimension until ten years ago, put the field in a productive era of its history. What is needed going forward is not more activity assays on unstudied species but strategic focus on existing resources: the hederagenin saponins of Clematis and anemoside B4 from Pulsatilla have received the formulation investment and pharmacokinetics characterisation that berberine was given, and the pharmacophylogenetic framework reviewed here is sufficiently validated to suggest that it could be expanded into the under-studied African and South Asian species of the family with reasonable, predictive certainty. A plant family that provides berberine, one of the few natural drugs to pass clinical testing for metabolic disease, and whose members are peppered with COX-2 inhibitors, saponins that disrupt biofilms, and alkaloids that activate Nrf2, with dozens of genera, should be considered a drug discovery system, not a botanical curiosity, and its systematic development is just beginning.

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