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Multidisciplinary Progress on *Alisma orientale* in Resources Chemistry, and Pharmacology

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Abstract

Alisma orientale (Sam.) Juzep. is a traditional medicinal herb whose modern research has revealed remarkable biological and pharmacological breadth. Studies on its germplasm diversity, ecological adaptation, and quality formation indicate that genetic background and environmental factors jointly shape its medicinal value. Chemically, *A. orientale* is characterized by abundant protostane-type triterpenoids—particularly alisol derivatives—along with diverse sesquiterpenoids, phenolics, alkaloids, polysaccharides, and proteinaceous components. These constituents collectively contribute to wide-ranging bioactivities. Pharmacological investigations demonstrate multi-system actions including regulation of lipid and glucose metabolism, protection of hepatic and renal systems, suppression of inflammatory and oxidative stress pathways, modulation of cardiovascular and platelet functions, and benefits in ocular and neurological disorders. Mechanistic studies highlight the involvement of key metabolic, inflammatory, and stress-responsive signaling networks that underlie these effects. In addition, multi-herb formulas containing *A. orientale* show synergistic therapeutic potential in metabolic diseases, renal injury, cardiovascular dysfunction, and neuroinflammatory conditions. Overall, the expanding body of evidence depicts *A. orientale* as a chemically complex, multi-target botanical resource with significant relevance for modern prevention and treatment of metabolic and inflammation-related disorders. Further integration of biological, phytochemical, and pharmacological insights will support its continued modernization and standardized clinical application.

Keywords

Alisma orientale, Genetic Resources, Chemical Constituents, Pharmacological Activity, Herb Combinations

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1. Introduction

Alisma orientale (Sam.) Juzep., the botanical source of Alismatis Rhizoma, occupies a central position in East Asian medical traditions where it is classified as a diuretic, dampness-resolving, and lipid-modulating herb. Over several decades, this medicinal plant has attracted sustained scientific interest because its pharmacological breadth extends far beyond traditional descriptions, encompassing metabolic regulation, hepatobiliary protection, renal modulation, cardiovascular activity, neuroprotection, and pronounced anti-inflammatory actions [1]-[4]. Parallel to advances in chemical isolation techniques and analytical profiling, research into *A. orientale* has revealed an extraordinarily rich chemical landscape dominated by protostane-type triterpenoids—such as alisol A, alisol B 23-acetate, alisol C derivatives, and related structural analogues—alongside a structurally diverse collection of sesquiterpenoids, diterpenoids, lignans, alkaloids, phenolics, polysaccharides, acidic glucans, and lectins [5] [6]. These metabolites contribute collectively to the plant's biological functions, and modern studies have shown that both purified single compounds and multi-component extracts participate in mechanisms relevant to human diseases.

Across pharmacological research, *A. orientale* displays a broad and multi-system therapeutic profile. Numerous in vivo and in vitro studies demonstrate regulatory effects on lipid and glucose metabolism, with improvements in NAFLD/NASH, MAFLD, and dyslipidemia mediated through pathways including PPARα activation, FXR modulation, suppression of ER stress, enhancement of hepatic iron homeostasis, and inhibition of lipotoxicity-induced apoptosis. Hepatobiliary and renal protection constitute another major research area, with compelling evidence that *A. orientale* triterpenoids modulate bile acid transport, inhibit NLRP3 inflammasome activation, suppress JAK2/STAT3 signaling, attenuate fibrosis, and regulate drug-metabolizing enzymes. Anti-inflammatory and antioxidant activities are consistently observed across organ systems—lung, liver, skin, periodontal tissues—via inhibition of NF-κB, iNOS, and cytokine expression, paralleled by enhancement of Nrf2-mediated antioxidant defenses. Additional studies highlight anticancer potential through apoptosis induction and mitochondrial disruption, melanogenesis inhibition via tyrosinase suppression, ocular protection mediated by TNF-α-linked pathways, and neuroprotective actions associated with glymphatic modulation and oxidative-stress resistance. Endophytic fungi associated with *A. orientale* further expand this pharmacological repertoire by producing metabolites that enhance stress tolerance and antioxidant capacity in model organisms.

A final dimension of contemporary research concerns multi-herb formulas containing *A. orientale*, reflecting its wide integration into traditional prescriptions. The classical Fuling-Zexie formula provides significant nephroprotection against hyperuricemia-induced renal injury by simultaneously inhibiting JAK2/STAT3 signaling and NLRP3 inflammasome activation. Cardiovascular formulas containing *A. orientale* exhibit potent antiplatelet effects, while network-based analyses of *A.*

orientale decoctions elucidate potential neuromodulatory mechanisms relevant to vertigo. These findings underscore the herb's mechanistic versatility: depending on its combinational context, *A. orientale* may act primarily on lipid metabolism, inflammatory signaling, renal excretory pathways, or neurovascular regulation.

Taken together, current research depicts *Alisma orientale* as a medicinal plant whose biological complexity extends across its genetic resources, ecological adaptability, and diverse chemical profile. Its hallmark protostane-type triterpenoids, accompanied by a broad array of sesquiterpenoids, phenolics, alkaloids, and macromolecular constituents, underpin extensive activities in metabolic regulation, inflammation control, hepatobiliary and renal protection, cardiovascular modulation, and neuro-ocular benefits. Studies spanning germplasm characterization, ecological determinants of quality, constituent chemistry, and mechanism-oriented pharmacology collectively illustrate that the therapeutic potential of *A. orientale* arises from coordinated, multi-target interactions rather than single-compound effects. Moreover, evidence from formulas containing *A. orientale* demonstrates synergistic actions in metabolic liver disease, hyperuricemia-related renal injury, vascular dysfunction, and neuroinflammatory disorders, reinforcing its importance within traditional multi-herb systems. This review consolidates these multidisciplinary advances to provide an updated, integrative perspective on *A. orientale* as both a chemically rich single herb and a versatile component of classical prescriptions.

2. Genomic Resources, Ecological Adaptation and Protostane Triterpene Biosynthesis

2.1. Germplasm Diversity and Molecular Identification

The genetic diversity and germplasm structure of *Alisma orientale* constitute the biological foundation for the plant's medicinal quality and ecological adaptability. Recent advances in molecular phylogenetics, chloroplast genomics, and DNA-based authentication have enabled clearer species delimitation within Alisma and more rigorous control over the identity of medicinal raw materials. Across these studies, researchers have applied chloroplast genome sequencing, ITS/trnL phylogenies, RAPD markers, PCR-RFLP assays, ARMS technology, and chemotype profiling to construct a multilayered understanding of germplasm variation. These approaches collectively demonstrate that *A. orientale* possesses notable intraspecific diversity and that accurate identification requires integrated genetic and chemical tools rather than morphological criteria alone.

High-resolution chloroplast genomic analysis has emerged as a powerful tool for resolving interspecific relationships in Alismataceae. Sequencing of complete chloroplast genomes from three Alismataceae species, including *A. orientale*, revealed distinct structural variation, repeat motif differences, and divergence hotspots that serve as effective DNA barcodes for species-level discrimination [7]. Earlier studies using RAPD markers and combined ITS and trnL sequences also supported the genetic distinctiveness of *A. orientale* within the genus, establishing

phylogenetic groupings consistent across nuclear and chloroplast loci [8]. Together, these findings highlight the evolutionary separation of *A. orientale* and provide a molecular framework for assessing germplasm relationships and potential domestication patterns.

Accurate authentication of *A. orientale* remains essential given its widespread use and vulnerability to substitution. A PCR-RFLP/ARMS-based method successfully distinguished *A. orientale* from its common adulterants by exploiting polymorphisms in species-specific loci, offering a rapid and reliable molecular diagnostic tool for quality control [9]. Beyond genetic markers, chemotype variation among regional germplasm has also been documented. A comparative analysis of rhizomes from different origins revealed significant differences in the content of angiotensin II and arginine vasopressin receptor-antagonistic terpenoids, suggesting that geographic or ecotypic divergence can manifest as distinct metabolite profiles [10]. These findings underscore that germplasm identification should integrate genetic and metabolic profiling to ensure consistency of medicinal quality.

Complementing molecular characterization, field-based evaluations offer essential insights into genotype × environment interactions and phenotypic stability. A multi-site, multi-year AMMI (Additive Main Effects and Multiplicative Interaction) analysis examined the yield and quality performance of different A. orientalis germplasm types, identifying significant G × E effects that shaped both biomass production and the stability of key medicinal traits [11]. This study demonstrated that some genotypes exhibit superior adaptability and consistent quality across environments, whereas others are more environmentally sensitive. By linking phenotypic stability with genetic background and regional growing conditions, the AMMI analysis provides valuable evidence that germplasm evaluation must consider both molecular identity and field performance. Importantly, it bridges laboratory-based authentication with real-world production constraints, laying the groundwork for improved breeding, conservation, and standardization strategies for *A. orientale*.

2.2. Environmental Drivers of Growth and Quality

Environmental conditions and ecological interactions exert profound influences on the growth performance, metabolite accumulation, and stress tolerance of *Alisma orientale*. As a wetland medicinal plant naturally adapted to hydrophilic habitats, *A. orientale* responds sensitively to water level, light intensity, soil microbiota composition, and pollutant exposure. Studies combining controlled-environment experiments, rhizosphere microbiome profiling, field ecological assessments, and pollutant uptake analyses have begun to clarify how these external factors shape not only plant vigor but also the production of medicinally important metabolites such as protostane-type triterpenoids.

Hydrological conditions represent a primary determinant of growth and survival in *A. orientale*. In a detailed submergence experiment, complete flooding was shown to significantly reduce plant height, biomass accumulation, and sur-

vival rate, yet the species displayed a notable capacity for recovery once aerial exposure was restored [12]. These results highlight an adaptive but costly tolerance mechanism consistent with the plant's wetland origin. Light availability exerts a complementary regulatory role: controlled light-intensity experiments demonstrated that low and moderate light conditions favored the accumulation of key protostane triterpenes, whereas excessive light suppressed metabolite production and altered carbon allocation patterns [13]. Together, these findings underscore that *A. orientale* integrates hydrological signals and light cues to balance growth and secondary metabolism, suggesting clear implications for agronomic optimization and standardized herbal production.

Soil environment and rhizosphere microbial composition form a second ecological dimension shaping *A. orientale* physiology. A field investigation across multiple production regions in Fujian, China revealed that soil physicochemical properties and fungal community structures were tightly linked to growth quality and root development, with specific fungal taxa positively associated with healthy plant morphology [14]. A broader rhizosphere metagenomic comparison across geographically distinct sites further demonstrated that microbial community composition and functional gene profiles differed significantly between regions, influencing nutrient assimilation, stress adaptation, and potentially metabolite accumulation [15]. These studies collectively emphasize that soil microbiome diversity is an overlooked but important contributor to the ecological quality formation of *A. orientale*, and that beneficial microbial associations may be leveraged to improve cultivation robustness.

Biotic and abiotic stress exposures add additional complexity to the plant's ecological resilience. A nationwide survey identified Fusarium proliferatum as the causal pathogen of spotting disease in *A. orientale*, marking the first report of this infection and highlighting the vulnerability of germplasm resources to emerging phytopathogens [16]. Conversely, endophytic microbial partners may provide protective benefits: indolecarbazole metabolites produced by Streptomyces sp. CNS-42, an endophyte associated with *A. orientale*, exhibited synergistic antifungal activity [17], suggesting that microbial symbionts may contribute to host defense. Abiotic pollution studies revealed that *A. orientale* can uptake and accumulate perfluorinated compounds such as PFOA and PFOS, with pollutant exposure causing alterations in intracellular biomolecule composition and detailing the plant's uptake mechanism, subcellular distribution, and stress-response patterns [18] [19]. These findings illustrate both the ecological adaptability and vulnerability of *A. orientale*, providing critical insights into environmental risks in medicinal-plant production systems.

Collectively, environmental and ecological studies demonstrate that *A. orientale* integrates hydrological, photic, edaphic, microbial, and pollutant-derived cues to regulate its survival, growth quality, and biosynthesis of key medicinal metabolites. Understanding these ecological determinants is essential for optimizing germplasm conservation, guiding cultivation practices, and ensuring consistent

medicinal quality under modern agricultural and environmental conditions.

2.3. Regulation of Protostane Triterpene Biosynthesis

Protostane-type triterpenes are the hallmark secondary metabolites of *Alisma orientale*, and a coherent regulatory framework for their biosynthesis has begun to emerge from integrated transcriptomic, proteomic, and functional gene studies. At the anatomical level, comparative transcriptome and metabolite profiling across four tissues—roots, rhizomes, leaves, and inflorescences—revealed strong spatial differentiation in both gene expression and triterpene accumulation [20]. Genes associated with isoprenoid and triterpene biosynthesis showed preferential expression in rhizomes and roots, consistent with the traditional use of the rhizome as the medicinal part and with higher local accumulation of protostane-type metabolites. This tissue-specific co-localization of biosynthetic gene expression and metabolite abundance provides a structural basis for considering protostane production as a developmentally and organ-specifically regulated process rather than a uniformly distributed metabolic event.

At the pathway level, key enzymes in the isoprenoid biosynthetic route have been functionally characterized and linked to protostane accumulation. Cloning and functional analysis of a 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) gene from *A. orientale* demonstrated that changes in its expression correlate with variations in protostane triterpene content, implicating HMGR as an important upstream control point in flux toward triterpenoid biosynthesis [21]. Transcriptome-guided mining further identified candidate genes associated with protostane-type triterpene biosynthesis, including oxidosqualene cyclases and downstream tailoring enzymes, providing a preliminary gene set for the triterpene biosynthetic network in *A. orientale* [22]. Elicitor studies with methyl jasmonate (MeJA) add a dynamic regulatory dimension: MeJA treatment significantly upregulated squalene epoxidase genes, leading to increased accumulation of protostane triterpenes and demonstrating that this enzyme family is responsive to jasmonate signaling and directly involved in controlling triterpene output [23].

Regulation extends beyond transcriptional control of individual enzymes to encompass microRNA- and protein-level mechanisms. A dedicated study on MeJA-induced regulation showed that specific microRNAs are differentially expressed in response to MeJA, targeting transcripts involved in the triterpene pathway and thereby fine-tuning the accumulation of protostane metabolites [23]. This implicates jasmonate-responsive microRNA networks as higher-order regulators that integrate stress or developmental cues with secondary-metabolite biosynthesis. Proteomic analysis following MeJA treatment further revealed coordinated changes in the abundance of enzymes associated with triterpene biosynthesis, redox homeostasis, and energy metabolism, indicating that elicitation triggers a broad reorganization of protein networks rather than a simple upregulation of a few pathway enzymes [24]. When viewed together, these findings describe a multi-layer regulatory system in which protostane triterpene biosynthesis in *A.*

orientale is controlled by: 1) tissue-specific expression of biosynthetic genes, 2) transcriptional activation of key upstream and pathway enzymes such as HMGR and squalene epoxidases, 3) microRNA-mediated post-transcriptional modulation, and 4) proteome-level adjustments in response to MeJA. This multi-level control framework provides a mechanistic basis for future efforts to optimize protostane production through breeding, elicitation strategies, or metabolic engineering.

3. Chemical Constituents and Analytical Characterization of *Alisma orientale*

3.1. Sesquiterpenoid Profiles and Discovery

Sesquiterpenoids constitute one of the most structurally diverse and chemically informative secondary-metabolite groups in Alisma orientale, encompassing both classical bisabolane-type frameworks and a range of highly modified, unusual carbon skeletons revealed through recent phytochemical investigations (**Figure 1**). Early structural investigations established the foundational chemotypes within the genus, particularly through the isolation and characterization of alismol, alismoxide, and related congeners [25]. These compounds, identified through conventional chromatographic separation followed by NMR and MS analysis, define the canonical sesquiterpenoid framework of *A. orientale* by exhibiting typical bisabolane ring systems with multiple oxidation states. Complementary work on the broader terpenoid fraction of the rhizome further confirmed the richness of sesquiterpenoids co-occurring with triterpenes and emphasized their taxonomic and chemotaxonomic significance within the Alismataceae [25]. The consistent presence of these core structures across early phytochemical studies provided a reference baseline from which later explorations could identify deviation, rearrangement, and novel biosynthetic diversification.

Recent investigations have considerably expanded the known sesquiterpenoid repertoire, demonstrating that *A. orientale* remains a prolific source of new structural entities. One study reported the isolation of ten previously undescribed sesquiterpenoids, all originating from the tuber, which showcased substantial variation in their oxidation patterns, cyclization modes, and stereochemical configurations [26]. These newly identified molecules extend well beyond the bisabolane archetype, revealing both rearranged and highly oxygenated skeletons that suggest either divergent enzymatic machinery or secondary modifications occurring late in biosynthesis. Parallel efforts have uncovered additional structurally unique molecules such as Orientalol L-P [27] and Alismanoid A [28], each representing significant departures from typical sesquiterpene frameworks. Orientalol L-P, for example, exemplifies a multi-oxygenated derivative displaying nephrotoxic effects in HK-2 cells, whereas Alismanoid A possesses a rare 1,2-seco bisabolene skeleton, indicative of carbon-carbon bond cleavage and atypical oxidative rearrangement. The discovery of these structurally divergent compounds highlights the ongoing potential of *A. orientale* to yield chemically unprecedented metabolites and un-

derscores the importance of comprehensive phytochemical mining using modern spectroscopic tools.

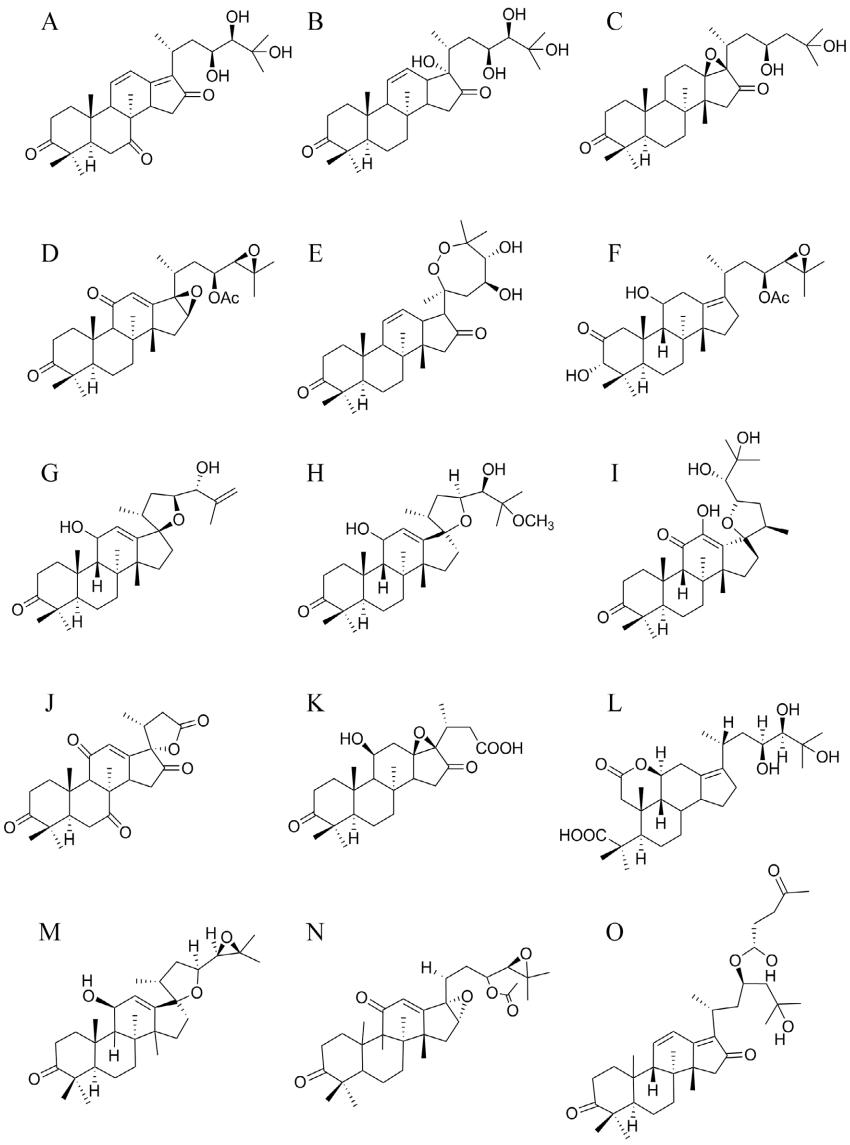

Figure 1. Representative terpenoid constituents isolated from Alisma orientale. The structures illustrate the major sesquiterpenes and protostane-type triterpenoids characteristic of the species, highlighting core scaffolds that underpin its pharmacologically active chemical profile. In the structures, OAc denotes an acetyl (-$OCOCH_3$) substituent.

Comparative analysis across these works reveals several broad conclusions regarding sesquiterpenoid diversity in *A. orientale*. First, the species consistently produces a core suite of bisabolane-derived compounds, which appear conserved across both rhizome and tuber material and across multiple decades of study [29] [30]. Second, more recent studies repeatedly uncover novel structures exhibiting rare skeletal modifications, suggesting that the species possesses a broader enzymatic repertoire than previously assumed [26]-[28]. Third, the biological evalua-

tions included in some of these studies—notably nephrotoxicity for Orientalol L-P and neuroprotective antioxidant activity for Alismanoid A—demonstrate that structural novelty often coincides with distinct bioactivities that diverge from those attributed to classical sesquiterpenes. Finally, studies examining mixed fractions of sesquiterpenoids and triterpenoids suggest potential synergistic or additive bioactivities, at least in vitro, particularly in inflammation-related assays such as nitric oxide inhibition [31]. Collectively, the accumulated findings depict *A. orientale* as a metabolically versatile species with a rich and evolving sesquiterpenoid landscape, making it a sustained source of novel natural products and an informative model for studying sesquiterpenoid biosynthetic diversification.

3.2. Protostane Triterpenes and Alisol Derivatives

Protostane-type triterpenoids constitute the most structurally defining and pharmacologically influential class of constituents in *Alisma orientale*, forming the chemical foundation upon which much of its medicinal relevance is built. Early phytochemical studies established the existence of a highly diverse protostane scaffold within the rhizomes and tubers of *A. orientale* and its related taxa, particularly A. plantago-aquatica subsp. orientale. Classic investigations such as the multi-part series "Studies on alismatis rhizoma I-III" demonstrated that the genus possesses an unusually rich array of tetracyclic triterpenoids distinguished by oxidative variations at C-11, C-23, and C-24, and by differences in side-chain truncation or substitution [32]-[34]. These foundational works delineated the major alisol-series compounds—alisol A, B, C, O, P, and their numerous acetates—establishing the protostane family as a hallmark chemical signature of the genus Alisma. Their common tetracyclic backbone, high degree of oxygenation, and the typical presence of acetyl or hydroxyl groups at key stereocenters quickly became chemotaxonomic markers for distinguishing *A. orientale* from its botanical relatives.

Building upon this foundation, numerous modern studies have significantly broadened the known protostane chemical space by describing both canonical alisol derivatives and structurally modified or truncated forms. For instance, Original Bioactive Triterpenoids from the Tuber of *A. orientale* reported new protostane derivatives with distinctive oxidation patterns and side-chain modifications that deviate from classical alisol frameworks [35]. Similarly, investigations into Protostane-Type Triterpenoids from *A. orientale* identified new analogues with rare structural features, including complex oxygen bridges and rearranged ring systems [36]. A further expansion of this chemical diversity is exemplified by the discovery of alisolide-type nor-protostane compounds—structures lacking carbons in the side-chain region—along with highly oxidized derivatives such as alisol B monoacetate and alisol C 23-acetate [37] [38]. These modifications indicate the presence of flexible enzymatic machinery capable of catalyzing both oxidative truncation and acylation, generating a diversified library of protostane frameworks with markedly different physicochemical and biological properties.

The discovery of Alismanin A, a C_{34} triterpenoid with an unusual truncated side chain and significant activity as a natural pregnane X receptor (PXR) agonist, demonstrates how far protostane structures can deviate from their classical forms while retaining or enhancing biological relevance [39]. Additional investigations into Allsolide, alisols O and P further illustrate the breadth of protostane diversification, showing that subtle variations in hydroxylation, acetylation, or double-bond positioning can produce compounds with distinct stereochemical configurations and potentially distinct pharmacological behaviors [40]. Complementary structural elucidation studies have provided crystallographic confirmation of absolute configurations in key alisol derivatives—most notably the stereostructure of 13,17-epoxy-alisol-B-23-acetate—highlighting the high stereochemical complexity embedded within the protostane backbone [41].

Comparative analysis across these studies reveals several overarching trends. First, *A. orientale* consistently yields a core set of protostane triterpenoids (alisol A/B/C-series), strongly conserved across plant materials and extraction methodologies. Second, modern investigations repeatedly uncover new structural variants, including ring-rearranged, side-chain-truncated, epoxy-bridged, or highly oxidized skeletons, indicating ongoing biosynthetic diversification. Third, structural modification often corresponds to shifts in biological activity: for example, alisol B 23-acetate and related acetates exhibit significant effects on drug-metabolizing enzymes and receptor signaling [42], while modified skeletons such as alismanin A demonstrate targeted receptor engagement. Finally, several studies combining triterpenoids and sesquiterpenoids in biological assays suggest that chemical diversity within *A. orientale* contributes to multi-target pharmacological profiles, particularly in inflammatory models that involve nitric oxide modulation [31].

Taken together, the protostane-type triterpenoids of *A. orientale* represent a chemically intricate and biologically potent family of natural products whose structural diversity continues to expand with ongoing research. Their complex biosynthetic modifications, well-resolved stereochemistry, and wide-ranging biological activities make this class a central focus for understanding the pharmacological efficacy and chemical identity of Alismatis Rhizoma.

3.3. Non-Terpenoid and Macromolecular Components

Although terpenoids dominate the phytochemical landscape of *Alisma orientale*, its non-terpenoid constituents represent an equally significant yet often underrecognized dimension of the plant's chemical diversity. These compounds include alkaloids, lignans, phenolic structures, simple organic acids, volatile constituents, polysaccharides, and lectins—each representing distinct biosynthetic origins and contributing to the broader pharmacological landscape of Alismatis Rhizoma. Among these, alkaloids and lignans have received renewed attention for their therapeutic potential. A study examining these constituents demonstrated that several alkaloids and lignans isolated from the rhizome exhibit significant anti-

pulmonary fibrosis activity by modulating apoptotic pathways and attenuating aberrant fibroblast behavior [43]. This finding not only broadens the spectrum of bioactive components in *A. orientale* beyond its well-characterized triterpenoids but also suggests that non-terpenoid small molecules may contribute to disease-specific efficacy through mechanisms complementary to those of protostane derivatives.

Phenolic compounds represent another important category of non-terpenoid constituents. Work on the seeds of *A. orientale* identified cis-aconitic anhydride ethyl ester along with several other phenolics, many of which possess structural motifs commonly associated with antioxidant or cytoprotective properties [44]. These seed-derived metabolites contrast with the primarily rhizome-derived terpenoids, indicating that different plant organs harbor distinct chemical repertoires with potentially different pharmacological roles. In addition to non-volatile phenolics, studies on the essential oil of *A. orientale*—derived from steam distillation of the tubers—revealed a mixture of volatile aromatic compounds with characteristic odor activity, including monoterpenoids, aromatic alcohols, and low-molecular-weight aldehydes [45]. Although traditionally overshadowed by the medicinal importance of triterpenoids, the essential-oil fraction provides chemical markers relevant for sensory quality evaluation and may contribute to minor physiological effects such as digestive stimulation or diuresis.

Macromolecular constituents add an additional layer to the chemical complexity of *Alisma orientale*. Early investigations documented the isolation and structural characterization of immunologically active polysaccharides from the tuber, including a glucan and a well-defined acidic polysaccharide, both exhibiting the capacity to modulate immune responses [46]. These polysaccharides, with high molecular weights and distinctive monosaccharide compositions, represent biosynthetic products fundamentally different from low-molecular-weight secondary metabolites. Their immunomodulatory properties align with a broader pattern observed among medicinal polysaccharides in other species, though in *A. orientale* the specific structural features responsible for activity—branching degree, uronic acid content, and glycosidic linkages—remain incompletely defined in existing reports. Complementing the polysaccharides, a novel lectin isolated from fresh rhizomes exhibited hemagglutination activity and demonstrated specificity toward particular carbohydrate residues [47]. As a proteinacious macromolecule with defined carbohydrate-binding domains, this lectin expands the biochemical landscape of *A. orientale* into the domain of plant defense proteins and highlights the presence of bioactive macromolecules rarely emphasized in pharmacognostic evaluations of the herb.

When viewed together, the non-terpenoid constituents of *A. orientale* demonstrate three overarching themes. First, they reveal significant organ specificity: lignans and alkaloids primarily originate from rhizomes, phenolics from seeds, and lectins from fresh roots, highlighting the need for organ-specific chemical profiling. Second, they encompass diverse biosynthetic pathways, ranging from

shikimate-derived phenolics to proteinaceous lectins, contrasting sharply with the mevalonate-dependent biosynthesis of the protostane triterpenoids. Third, they contribute distinct and sometimes complementary biological activities, including immunomodulation, antioxidant effects, and anti-fibrotic actions—activities that cannot be attributed solely to the triterpenoid fraction. Although historically overshadowed by the prominence of protostane-type compounds, the non-terpenoid and macromolecular constituents of *Alisma orientale* clearly show that the species possesses a multifaceted chemical profile whose therapeutic potential extends well beyond its signature triterpenoids.

3.4. Analytical and Chemometric Approaches for Marker Identification

Analytical research on *Alisma orientale* has progressively evolved from classical isolation-based phytochemistry toward a technologically sophisticated framework integrating high-resolution mass spectrometry, chemometrics, and targeted quantitative assays. Contemporary chromatographic and spectrometric methodologies have greatly accelerated the structural elucidation of triterpenoids, sesquiterpenoids, and other constituents of *Alisma orientale*, while simultaneously providing deeper insights into their functional relationships, quality markers, and potential in vivo significance.

High-resolution mass spectrometry, particularly LC-QTOF-MS/MS, has become central to defining the chemical architecture of *A. orientale* decoctions and extracts. A representative example is the systematic characterization of hypolipidemic constituents using LC-QTOF-MS/MS, which provided structural assignments for multiple protostane-type triterpenoids by generating diagnostic fragmentation patterns—most notably the neutral loss of water, acetyl groups, and side-chain cleavage signatures characteristic of the alisol family [6]. This work established a mass-spectrometric fingerprint for pharmacologically active triterpenoids in aqueous decoctions, bridging traditional preparation methods with modern analytical standards. Complementary structural elucidation studies, such as the classification of major triterpenoids based on combined chromatographic retention behavior and MS fragmentation, have enabled rapid identification of alisol derivatives across raw and processed materials [48]. These classification tools are particularly valuable for distinguishing structurally similar acetates and oxo-derivatives whose spectra differ by only subtle fragment ions. Additional investigations relying on NMR and crystallographic methods—for example, the determination of the absolute stereochemistry of 13,17-epoxy-alisol-B-23-acetate [41]—further validate the MS-based assignments and highlight the degree of stereochemical intricacy present in Alisma triterpenoids.

Analytical methods have also expanded beyond structural elucidation to quantify marker constituents and evaluate their pharmacological contributions. UFLC/MS/MS and LC-MS/MS methods have been developed to simultaneously determine key alisol derivatives in biological matrices, enabling pharmacokinetic

analysis and facilitating correlation with bioactivity. A UFLC/MS/MS protocol for simultaneous quantitation of alisol A and alisol B 23-acetate demonstrated high sensitivity and specificity in rat plasma [49], while a more sensitive LC-MS/MS method enabled simultaneous detection of alisol A and alisol A 24-acetate at low nanogram levels [50]. These targeted assays are indispensable for assessing systemic exposure, metabolic fate, and dose-response relationships of representative triterpenoids—an essential step for translating phytochemical complexity into pharmacological relevance.

Chemometric strategies have added a higher-order interpretive layer to these analytical methods by integrating quantitative chemical data with pharmacological outcomes. A landmark biochemometrics study combined quantitative determination of triterpenoids with functional diuretic assays to identify constituents most strongly associated with diuretic activity in crude and processed materials [51]. By correlating multivariate chemical profiles with biological endpoints, the study uncovered potential diuretic-driving compounds and demonstrated how chemical variation introduced by processing influences pharmacological performance. This approach moves beyond traditional single-component evaluation by offering a statistically grounded method for identifying synergistic clusters, redundancy in chemical profiles, and candidate quality markers.

Together, these analytical and chemometric developments underscore several key trends in contemporary *A. orientale* research. First, structural characterization is increasingly driven by mass spectrometry-centered workflows that shorten discovery timelines and improve accuracy. Second, quantitative methods now support pharmacokinetic and mechanistic studies, enabling a more rigorous evaluation of bioactive components. Third, chemometrics provides the statistical infrastructure necessary to link complex multi-component chemistry with functional outcomes, thereby laying the groundwork for evidence-based quality-marker (Q-marker) development. As a result, the analytical landscape for *A. orientale* has shifted from descriptive phytochemistry to an integrated platform capable of supporting quality control, mechanistic pharmacology, and modernization of traditional medicinal practice.

4. Pharmacological Activities and Mechanistic Insights of *Alisma orientale*

4.1. Metabolic Regulation in NAFLD, NASH and Dyslipidemia

A growing body of evidence demonstrates that *Alisma orientale* and its protostane-type triterpenoids exert multi-layered regulatory effects on lipid homeostasis, glucose metabolism, and the pathological progression of metabolic dysfunction-associated conditions such as NAFLD, NASH, and hyperlipidemia (**Figure 2**). These metabolic effects have been elucidated through a wide range of methodological approaches, including rodent models of diet-induced steatosis, meta-analyses of preclinical metabolic studies, lipidomics-based pathway interpretation, network pharmacology analyses, and targeted functional validation in cellu-

lar systems. A systematic meta-analysis of rodent models integrating 42 studies found that extracts of Alismatis Rhizoma significantly improved fasting blood glucose, plasma triglycerides, total cholesterol, and LDL-C, while also reducing body weight and hepatic steatosis scores, indicating that the herb's metabolic benefits are robust across different extraction methods, dosages, and animal models [52]. These findings provide quantitative support for the long-standing traditional use of *A. orientale* in managing lipid accumulation and dampness-related metabolic conditions.

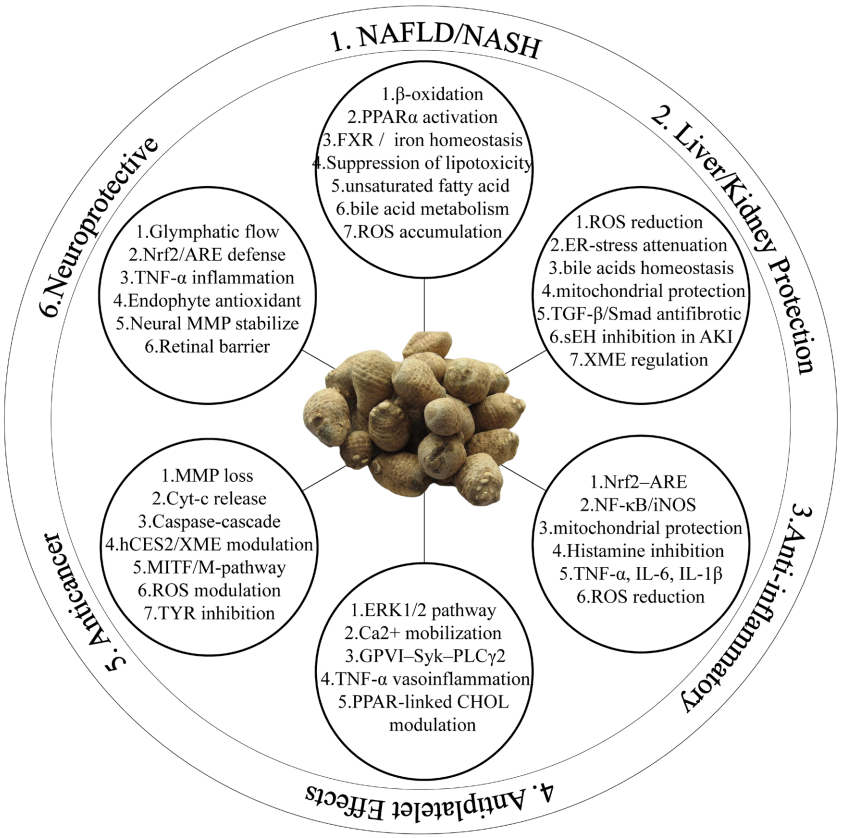

Figure 2. Overview of the pharmacological activities of Alisma orientale and the proposed molecular mechanisms underlying its bioactions. The schematic summarizes key regulatory pathways implicated in its hepatoprotective, renoprotective, metabolic, anti-inflammatory, antioxidative, neuroprotective, and immunomodulatory effects, including modulation of lipid metabolism, bile acid homeostasis, mitochondrial function, oxidative stress responses, inflammatory signaling, and barrier stabilization.

Several mechanistic studies converge on nuclear receptor signaling and fatty acid oxidation as central therapeutic pathways. An extract of *A. orientale* markedly ameliorated NASH in a murine model by activating PPAR*α*, which led to enhanced *β*-oxidation and reduced hepatic lipid deposition, thereby attenuating inflammation and fibrosis characteristic of advanced metabolic fatty liver disease [53]. Complementing these results, a study in MAFLD mice demonstrated that Alisma Orientalis Extract restored disrupted hepatic iron metabolism by suppressing aberrant

FXR-mediated transcription, ultimately mitigating steatosis and improving overall hepatocellular metabolic function [54]. At the systems level, a lipidomics-guided phenotype study revealed coordinated regulation of lipid metabolic networks—including acylcarnitine turnover, phospholipid remodeling, and bile acid biosynthesis—in a chronic kidney disease model, implicating broad lipid-governing pathways beyond the liver alone [55]. These studies collectively highlight that *A. orientale* constituents act at multiple metabolic nodes, particularly PPARα and FXR signaling, to reprogram lipid utilization and limit lipotoxicity.

Network pharmacology and metabolomics analyses further reveal the multi-target, multi-pathway nature of metabolic regulation by *A. orientale*. A mechanistic investigation integrating compound-target prediction with molecular docking identified interactions between Alisma-derived constituents and key enzymes of cholesterol biosynthesis, fatty acid desaturation, and inflammatory modulation, providing a molecular-level map that complements in vivo metabolic outcomes [56]. Similarly, an integrated metabolomics and lipidomics study in hyperlipidemic mice identified suppression of pathways related to glycerophospholipid metabolism, unsaturated fatty acid biosynthesis, and oxidative stress response, demonstrating that Alisma preparations modulate both upstream anabolic lipid pathways and downstream oxidative/inflammatory sequelae [57]. Evidence from cellular models aligns with these systemic findings: extracts of *A. orientale* protected HepG2 cells from non-esterified fatty acid-induced lipoapoptosis by restoring mitochondrial integrity, suppressing ROS accumulation, and normalizing lipid-handling gene expression [58]. Additional pharmacokinetic and lipidomic data suggest that triterpenoid metabolites may act additively or synergistically to influence metabolic pathways shaping lipid deposition, oxidative balance, and adipokine regulation [59] [60].

Together, these studies illustrate a coherent mechanistic narrative: *Alisma orientale* ameliorates metabolic disease by enhancing fatty acid oxidation (PPARα), improving bile acid and cholesterol metabolism (FXR and downstream pathways), normalizing hepatic iron homeostasis, and counteracting lipotoxic apoptosis and oxidative stress. The convergence of animal, cellular, lipidomic, and chemoinformatic evidence across multiple studies—with supportive quantitative outcomes from meta-analysis—indicates that *A. orientale* exerts its metabolic benefits through integrated reprogramming of lipid and glucose metabolism rather than through single-target modulation. This multi-pathway regulation reinforces its therapeutic potential in NAFLD/NASH and broader metabolic syndrome.

4.2. Hepatic, Biliary and Renal Protection

A substantial body of work demonstrates that *Alisma orientale* and its protostane-type triterpenoids exert broad protective actions across hepatic, biliary, and renal systems, acting through pathways that converge on inflammation, oxidative stress, mitochondrial integrity, bile acid signaling, and xenobiotic metabolism (**Figure 2**). These effects have been investigated using diverse model systems—

including diet-induced metabolic disease, chemically induced hepatic or renal injury, cholestasis models, and in vitro enzyme assays—yielding a multifaceted mechanistic profile. A study in MAFLD mice revealed that Alisma Orientalis Extract improved hepatic iron deregulation and corrected associated metabolic impairments by suppressing aberrant FXR-mediated gene activation, thereby restoring bile acid and iron homeostasis under conditions of chronic metabolic stress [54]. In parallel, a pharmacological evaluation of *A. orientale* constituents in an in vitro cholestasis model showed that protostane derivatives activated FXR directly, leading to improvements in bile acid transport, reduced hepatocellular stress, and reversal of cholestatic markers [55]. These convergent findings underscore FXR as a central molecular target, through which *A. orientale* modulates both bile acid turnover and metabolic resilience in hepatocytes.

Beyond bile acid regulation, multiple studies demonstrate that *A. orientale* protects hepatic tissue from chemical or metabolic insults by modulating oxidative and endoplasmic reticulum (ER) stress. In a murine model of hepatic steatosis, *A. orientale* extract attenuated ER stress responses by downregulating PERK and IRE1α pathways, thereby reducing lipid-induced hepatocyte injury [2]. Additional work exploring the protective effects of *A. orientale* polysaccharides found that treatment led to reductions in liver fibrosis markers and inhibition of TGF-β-mediated profibrotic signaling, indicating that non-terpenoid macromolecules also confer hepatoprotective benefits [61]. These molecular activities align with earlier evidence demonstrating that alisol B 23-acetate modulates hepatic drug-metabolizing enzymes in rats treated with bromobenzene—a classical hepatotoxin—resulting in partial restoration of metabolic enzyme activities and improved antioxidative capacity [25]. Collectively, these studies illustrate that *A. orientale* mitigates hepatotoxicity by regulating ER stress, maintaining redox balance, modulating fibrogenesis, and supporting metabolic enzyme integrity under toxic challenge.

Renal protection represents another major pharmacological domain for *A. orientale*, with studies demonstrating significant benefits in both acute and chronic injury models. A triterpenoid-rich extract exerted pronounced nephroprotective effects in chronic kidney disease (CKD) by regulating lipid metabolic pathways, suppressing oxidative stress, and improving renal structural integrity—mechanisms revealed through integrative lipidomics and phenotype analysis [62]. Similarly, *A. orientale* extract alleviated acute kidney injury by inhibiting apoptosis, dampening inflammatory responses, and reducing oxidative stress in a cisplatin-induced renal injury model, where modulation of soluble epoxide hydrolase (sEH) played a central mechanistic role [63]. Further evidence from a study on experimental renal fibrosis demonstrated that *A. orientale* attenuated excessive extracellular matrix deposition by inhibiting the Smad2/3 pathway downstream of TGF-β signaling, offering molecular insight into how the herb interrupts fibrotic remodeling [64]. Complementary work on herbal formulations containing *A. orientale*—including diuretic herbal pairs and multi-herb prescriptions—confirms

that Alisma-derived triterpenoids synergize with other botanical constituents to enhance renal function, regulate electrolyte balance, and reduce inflammatory infiltration in kidney tissue [65] [66].

A final mechanistic layer involves the herb's regulatory effects on xenobiotic metabolism. Studies examining enzyme modulation reveal that alisol B derivatives influence the activity of phase I and phase II hepatic enzymes, altering metabolic processing of xenobiotics and enhancing cellular resilience under chemical insult [25]. These findings are consistent with broader evidence that *A. orientale* extracts promote detoxification-associated pathways and modulate drug-metabolizing enzymes—an activity that may contribute to both hepatoprotective and nephroprotective outcomes. Notably, the herb's modulation of FXR and sEH suggests that its xenobiotic-regulatory actions extend beyond classical detoxification enzymes, intersecting with lipid metabolism, bile acid transport, and inflammatory signaling.

Together, the evidence across these studies reveals a coherent pharmacological profile in which *A. orientale* supports hepatic, biliary, and renal health through coordinated mechanisms involving nuclear receptor activation, stress-pathway modulation, anti-fibrotic actions, and regulation of xenobiotic metabolism. The convergence of findings from metabolomics, molecular docking, enzyme assays, and in vivo pathology underscores *A. orientale* as a multi-target therapeutic agent with broad relevance for liver and kidney diseases.

4.3. Anti-Inflammatory and Antioxidant Actions across Organs

Extensive research demonstrates that *Alisma orientale* and its bioactive constituents exert potent anti-inflammatory and antioxidant effects across multiple organ systems, including the lung, liver, skin, and periodontal tissues (**Figure 2**). These effects arise from coordinated regulation of oxidative stress pathways, inflammatory cytokine signaling, epithelial barrier integrity, and cellular apoptosis. A wide array of extract types—including protostane-type triterpenoids, sesquiterpenoids, polysaccharides, and alkaloid- or lignan-rich fractions—has been evaluated across diverse disease models, such as acute lung injury, COPD-like inflammation, hepatic damage, skin hypersensitivity, and periodontitis. Such methodological diversity provides a broad mechanistic understanding of how different classes of Alisma constituents converge on shared immune-modulating axes.

Lung-protective effects represent one of the most consistently reported activities. Ethanol extract of *A. orientale* significantly reduced pathological lung changes in a murine COPD model by suppressing inflammatory cell infiltration and downregulating inflammatory mediators, suggesting that the extract directly attenuates chronic airway inflammation [67]. Likewise, isolated sesquiterpenoids and triterpenoids demonstrated inhibition of nitric oxide production in LPS-activated macrophages, revealing direct suppression of inducible nitric oxide synthase (iNOS) and confirming the anti-inflammatory potential of purified constituents [31]. Another study showed that purified alismol and related compounds reduced oxidative stress in pulmonary tissues, acting partly through the Nrf2 pathway [68].

These complementary findings demonstrate that both crude extracts and single-compound isolates from *A. orientale* regulate airway inflammation through shared mechanisms involving iNOS suppression, downregulation of pro-inflammatory cytokines, and reinforcement of antioxidant defenses.

Anti-inflammatory and antioxidant actions are also prominent in hepatoprotection. A phytochemical study evaluating alkaloids and lignans isolated from *A. orientale* demonstrated significant antifibrotic and anti-inflammatory effects through modulation of apoptotic pathways in hepatic stellate cells, indicating that non-terpenoid constituents also participate in liver protection [43]. In parallel, anti-inflammatory triterpenoids isolated from A. plantago-aquatica subsp. orientale were shown to reduce ROS accumulation and inhibit NF-κB activation, thereby limiting oxidative injury and hepatocellular inflammation [34]. These results complement polysaccharide-mediated hepatoprotection reported in complementary studies, where inhibition of inflammatory cytokines and improvement of antioxidative capacity also played central roles [61]. Collectively, these findings emphasize that *A. orientale* acts on both early oxidative pathways and downstream inflammatory signaling to mitigate hepatic injury.

Dermatologic and mucosal protective actions also form an important component of *A. orientale*'s pharmacological profile. A study on experimental atopic dermatitis demonstrated that Alisma rhizome extracts markedly suppressed mast-cell activation, inhibited histamine release, and reduced inflammatory cytokines, providing clear evidence for its benefits in allergic skin inflammation [69]. Similar anti-inflammatory effects were reported in a murine contact dermatitis model, where triterpenoid constituents attenuated leukocyte infiltration and normalized epidermal architecture by suppressing cytokine-driven inflammatory cascades [10]. In periodontal disease, a formulation containing *A. orientale* inhibited lipopolysaccharide-induced inflammation in human periodontal ligament cells and reduced oxidative stress-induced tissue damage, suggesting potential therapeutic roles in oral inflammatory disorders [70].

Comparative examination across these studies reveals a unifying mechanistic theme: *A. orientale* suppresses inflammation via coordinated inhibition of NF-κB signaling, iNOS expression, and pro-inflammatory cytokine production, while simultaneously enhancing Nrf2-mediated antioxidant defenses and mitigating oxidative damage. These convergent pathways explain why *A. orientale* demonstrates protective effects across diverse tissues and inflammatory contexts—including pulmonary, hepatic, dermal, and periodontal systems. The breadth of evidence indicates that the anti-inflammatory and antioxidant properties of *A. orientale* are neither tissue-specific nor limited to a single class of constituents, but instead represent a generalized pharmacological signature emerging from multi-component, multi-target interactions.

4.4. Cardiovascular and Antiplatelet Effects

A recurring pharmacological theme emerging from multiple studies is the cardi-

oprotective and antiplatelet potential of *Alisma orientale* and its characteristic protostane-type triterpenoids. These activities are mediated through coordinated modulation of platelet activation pathways, inflammatory mediators involved in vascular dysfunction, and signaling mechanisms that influence lipid metabolism and endothelial integrity. Across cell-based experiments, animal models, and network-based mechanistic analyses, the evidence positions *A. orientale* as a multi-target botanical agent capable of regulating hemostasis, vascular inflammation, and atherosclerosis-relevant processes.

Direct antiplatelet effects have been demonstrated using both purified compounds and multi-herb formulations containing *A. orientale*. An optimized herbal combination including *Scutellaria baicalensis*, *Alisma orientale*, and *Atractylodes japonica* exhibited potent inhibition of platelet aggregation and thrombus formation by suppressing key platelet activation pathways such as collagen-induced aggregation and ADP-mediated signaling. The formulation reduced intracellular calcium mobilization and downregulated markers of platelet activation, suggesting that *A. orientale* contributes to the modulation of early platelet-signaling events. These results align with findings from an *A. orientale* ethanol extract, which inhibited platelet activation through regulation of glycoprotein VI (GPVI) and downstream Syk-PLCγ2 signaling, demonstrating that Alisma-derived constituents directly interfere with collagen-mediated platelet activation cascades [4]. Taken together, these studies show that *A. orientale* possesses intrinsic antiplatelet properties that are mechanistically tied to the suppression of GPVI-dependent platelet activation—an important therapeutic target in the prevention of thrombosis.

Beyond direct platelet modulation, *A. orientale* also exerts broader cardiovascular benefits through lipid-regulatory and anti-inflammatory mechanisms relevant to atherosclerosis and metabolic cardiovascular risk. A network pharmacology and molecular docking analysis demonstrated that Alisma constituents—particularly protostane triterpenoids—interact with targets involved in cholesterol metabolism, vascular inflammation, and endothelial dysfunction, including PPAR isoforms, TNF-α, and key enzymes in lipid biosynthesis [72]. The computational predictions supported experimental findings in related metabolic studies showing improved lipid profiles and decreased inflammatory mediators following Alisma treatment [52] [56]. In vascular smooth muscle cells, alisol derivatives were shown to inhibit Ox-LDL-induced phenotypic switching and migration—pathological processes central to vascular remodeling and plaque development—via downregulation of ERK1/2 signaling [56]. This inhibitory action on ERK1/2 further underscores how *A. orientale* modulates not only lipid metabolism but also the cellular behaviors contributing to atherosclerotic progression.

Several studies suggest that the cardiovascular benefits of *A. orientale* arise from the intersection of its antiplatelet, lipid-lowering, and anti-inflammatory actions. The same protostane triterpenoids that inhibit platelet activation also regulate cholesterol handling and oxidative stress, supporting a cohesive mechanistic

model where improvements in vascular homeostasis emerge from simultaneous modulation of multiple risk-related pathways. Moreover, herbal formulas containing *A. orientale* display enhanced antithrombotic effects relative to individual components, implying synergistic interactions between Alisma-derived triterpenoids and flavonoids from companion herbs. This multi-component synergy reflects the systems-level therapeutic potential of *A. orientale*, particularly in multifactorial cardiovascular conditions.

Collectively, the evidence reviewed here demonstrates that *A. orientale* exerts significant cardiovascular and antiplatelet activity by targeting platelet activation pathways (GPVI-Syk-PLCγ2 axis), suppressing vascular smooth muscle cell remodeling (ERK1/2), improving lipid profiles, and modulating inflammatory mediators. These convergent mechanisms position *A. orientale* as a promising botanical candidate for the prevention and treatment of thrombosis, atherosclerosis, and related cardiovascular disorders.

4.5. Anticancer and Pigmentation-Modulating Activities

A distinct subset of *Alisma orientale* pharmacological research focuses on its anticancer and melanogenesis-regulating properties, largely driven by the bioactivity of protostane-type triterpenoids such as alisol derivatives. These compounds demonstrate potent actions across multiple cellular processes—apoptosis induction, mitochondrial dysfunction, modulation of oxidative stress, and enzyme inhibition—suggesting potential multi-target activities for oncology and pigment-disorder research. Investigations using diverse experimental models—including human prostate cancer, lung cancer, and melanoma cell lines, as well as enzymatic systems relevant to xenobiotic metabolism—collectively provide mechanistic insights into how Alisma-derived molecules modulate carcinogenic pathways.

The anticancer activity of *A. orientale* has been most thoroughly characterized in prostate and lung cancer models. A clinical-oriented investigation into *A. orientale* extract reported beneficial effects in men with symptoms associated with prostate disease, supported by in vitro evidence showing that the extract suppresses proliferation and induces apoptosis in prostate cancer cell lines [3]. Mechanistically, alisol B-23-acetate—one of the major protostane triterpenoids—induces apoptosis in human lung cancer cells through a mitochondrial pathway characterized by cytochrome c release, caspase activation, and disruption of mitochondrial membrane potential [73]. This mitochondrial-dependent cell death underscores a central theme in Alisma anticancer pharmacology: the capacity of protostane triterpenoids to target intrinsic apoptotic machinery. Additionally, triterpenoid fractions from *A. orientale* have been shown to suppress viability in multiple cancer cell lines, aligning with these mechanistic insights and suggesting a generalizable mode of anticancer action across diverse cellular contexts [74].

Melanogenesis modulation represents another important pharmacological domain in which *A. orientale* triterpenoids exert notable effects. A study investigat-

ing alisol B—a representative protostane triterpenoid—revealed strong inhibition of melanin production in murine B16 melanoma cells, mediated by downregulation of tyrosinase activity and suppression of melanogenic signaling pathways [75]. The reduction in melanin synthesis was accompanied by decreased expression of key melanogenic genes, implying transcriptional regulation of melanocyte function. Supporting evidence from related investigations demonstrates that triterpenoids from *A. orientale* not only impact pigmentation pathways but also modulate oxidative stress responses in melanocytes—an effect relevant to both hyperpigmentation disorders and melanoma progression.

Several non-terpenoid constituents also contribute to anticancer activity, particularly through modulation of xenobiotic metabolism. Studies examining Alisma-derived compounds have demonstrated inhibitory effects on human carboxylesterase 2 (hCES2)—a drug-metabolizing enzyme involved in prodrug activation and detoxification—suggesting that certain triterpenoids and related constituents may alter drug sensitivity or modulate carcinogen processing [62]. Earlier work further confirmed that alisol B and its derivatives influence liver drug-metabolizing enzymes under toxicological challenge [25]. These findings highlight a mechanistic intersection between anticancer activity and xenobiotic metabolism, implying that *A. orientale* constituents may enhance anticancer therapy either directly—via apoptosis induction—or indirectly through modulation of metabolic enzymes that govern drug activation.

Overall, the anticancer and melanogenesis-modulating activities of *Alisma orientale* arise from a combination of direct cytotoxic actions, mitochondrial dysfunction and apoptotic signaling, suppression of melanogenic pathways, and modulation of xenobiotic metabolism. Together, the evidence suggests that Alisma-derived triterpenoids constitute a versatile pharmacophore with potential translational relevance, which remains to be established and requires in vivo exposure-activity validation.

4.6. Neuroprotective and Ocular Benefits

Although *Alisma orientale* is best known for its metabolic and diuretic indications, emerging evidence highlights a growing role in neuroprotection and ocular health. These effects are mediated by both small-molecule triterpenoids and bioactive metabolites produced by endophytic fungi associated with the plant. Collectively, studies in this area employ a diverse toolkit—ranging from UPLC-Triple-TOF/MS-guided component identification and network pharmacology, to zebrafish ocular disease models, murine models of obesity-related cognitive impairment, and Caenorhabditis elegans as an oxidative stress model organism. Together, these approaches provide mechanistic insight into how *A. orientale* and its associated microbiome modulate neuroinflammatory pathways, oxidative-stress responses, and tissue-specific protection in the eye and brain.

The ocular protective potential of *A. orientale* has been elucidated through the identification and functional validation of alisol A as an "eye-entering" ingredient.

In a study combining UPLC-Triple-TOF/MS, network pharmacology, and zebrafish experimentation, alisol A was identified as a key component absorbed into ocular tissue after oral administration of *A. orientale* extract and shown to relieve macular edema through modulation of TNF-α-associated pathways [76]. Network pharmacology predicted that alisol A targets inflammatory mediators and signaling nodes related to vascular permeability, which was subsequently supported by zebrafish models in which AO-derived treatment reduced macular edema-like retinal changes and downregulated TNF-α-linked inflammatory responses [76]. This multi-layered strategy—chemical profiling to identify eye-accessible constituents, computational target prediction, and in vivo functional validation—supports the possibility that AO-derived triterpenoids, particularly alisol A, exert direct anti-inflammatory and vasoprotective actions within ocular tissues.

Neuroprotective effects have been investigated in the context of obesity-associated cognitive impairment, a condition increasingly recognized as a metabolic-neurological interface disorder. An ethanol extract of *A. orientale* (EEAO) was evaluated in a high-fat diet-induced obesity model, where cognitive deficits were linked to enhanced neuroinflammation and impaired glymphatic function [77]. The study revealed that obesity promoted neuroinflammation in part through glymphatic-system dysregulation, leading to the accumulation of neurotoxic metabolites and exacerbated inflammatory signaling in the brain. EEAO significantly alleviated cognitive impairment, improved glymphatic clearance function, and suppressed central inflammatory mediators, while concurrently ameliorating abnormal systemic glucose and lipid metabolism [77]. These findings position *A. orientale* as a promising candidate for targeting the gut-liver-brain axis of obesity-related cognitive dysfunction, acting at the intersection of peripheral metabolic regulation, glymphatic clearance, and central neuroinflammatory control.

Additional evidence linking *A. orientale* to neuroprotective potential arises from the activities of its associated endophytic fungi. Chaetomium globosum isolated from *A. orientale* was shown to enhance the antioxidative-stress capacity of Caenorhabditis elegans by stimulating endogenous antioxidant defense mechanisms [68]. Treatment with fungal metabolites increased survival under oxidative stress, elevated antioxidant enzyme activities, and promoted the expression of stress-response genes, indicating a robust upregulation of cellular defense pathways [68]. Given the central role of oxidative stress in neurodegenerative processes, these results suggest that *A. orientale*-associated endophytes may complement plant-derived triterpenoids by reinforcing systemic and neuronal resilience to redox imbalance. Taken together, the ocular and neuroprotective findings from these studies delineate a broader functional profile in which both *A. orientale* and its microbiome-derived metabolites modulate TNF-α-driven inflammation, glymphatic-mediated neuroinflammatory cascades, and oxidative-stress defenses, positioning the plant as a promising source of multi-target interventions for ocular and central nervous system disorders.

5. Therapeutic Applications of *Alisma orientale*-Containing Formulas

5.1. *Alisma orientale*-Containing Chinese Herbal Formulas in Metabolic Liver Diseases and Lipid Dysregulation

Across NAFLD/NASH/MASH models, Alisma orientale-containing formulas consistently improve hepatic steatosis and inflammatory injury (Table 1). The reported mechanisms largely converge on three recurring modules: gut-liver barrier dysfunction with innate immune activation (TLR4/NF-κB), oxidative-stress control (Nrf2) coupled to inflammasome/pyroptosis inhibition (NLRP3-caspase-1/GSDMD), and cellular stress adaptation programs such as autophagy and tissue-remodeling signaling (e.g., Hippo-YAP/TAZ). In Western-diet-induced MASH, suppression of aberrant Hippo-YAP/TAZ activity has been linked to reduced steatosis, inflammation, and fibrosis (e.g., Injinoryeong-san) [78]. Multiple NAFLD studies also support the gut-liver axis as a key intervention point, where restoration of intestinal tight junction integrity and attenuation of TLR4/NF-κB signaling in gut and liver accompany improved hepatic pathology (e.g., Qingre Quzhuo Capsule; Dahuang Zexie Decoction) [79] [80].

Table 1. Chinese herbal formulas containing alisma orientale and their clinical uses.

Chinese herbal compound	Main Compositions	Clinical application	References
Zexie decoction	*Alisma orientale*, *Atractylodes macrocephala*	Regulate sugar and lipid metabolism	[89]
Modified Zexie Decoction	*Alisma orientale*, *Atractylodes macrocephala*, *crataegi fructus*	Antihypertensive and anti-inflammatory	[88]
Fuling -Zexie formula	*Poria cocos*, *Pueraria lobate*, *Alisma orientale*, *Atractylodes macrocephala*	Ameliorate hyperuricemia and its associated renal injury	[86]
Danshen Zexie Decoction	*Salvia miltiorrhiza*, *Alisma orientale*, *Atractylodes macrocephala*	Regulating lipid mechanism	[81]
Dahuang Zexie Decoction	*Alisma orientale*, *Atractylodes macrocephala*, *Rheum palmatum*	Obviously mitigate NAFLD and decrease blood lipid levels	[80]
Chaize mixture	*Bupleurum chinense*, *Scutellaria baicalensis Georgi*, *Pinellia ternata*, *Codonopsis pilosula*, *Glycyrrhiza uralensis*, *Zingiber officinale*, *Ziziphus jujuba*, *Atractylodes macrocephala*, *Alisma orientale*	Metabolic disorders; hyperlipidemia among middle-aged adults	[82]
Siling decoction	*Poria cocos*, *Polyporus umbellatus*, *Alisma orientale*, *Atractylodes macrocephala*	Clear heat, drain dampness, relieve diarrhea.	[87]
Qi pi pill	*Panax ginseng*, *Atractylodes macrocephala*, *Poria cocos*, *Glycyrrhiza uralensis Fisch*, *Citrus reticulata Blanco*, *Dioscorea opposite*, *Nelumbo nucifera*, *Crataegus pinnatifida*, *Liushenqu*, *Hordeum vulgare*, *Alisma orientale*	Prevention and treatment of influenza infection	[90]
PingTang No.5 capsule	*Alisma orientale*, *Rheum palmatum*, *Atractylodes macrocephala*, *Polygonum multiflorum*, *Crataegi Fructus*	Lipid metabolism disorder	[84]

Continued

Liuwei Dihuang decoction	*Rehmannia glutinosa*, *Dioscorea opposite*, *Cornus officinalis Sieb*, *Paeonia suffruticosa*, *Alisma orientale*, *Poria cocos*	Various diseases with characteristic features of kidney yin deficiency	[91]
Jianpi Huoxue Formula	*Atractylodes macrocephaly*, *Salvia miltiorrhiza*, *Rasux Paeonia*, *Alba Alisma orientale*, *Fructus Schisandrae Chinensis*	Nonalcoholic fatty liver disease	[83]
preparation Tongqiao Jiannao capsules	*Alisma orientale*, *Atractylodes macrocephaly*, *Carthami Flos*, *Salvia miltiorrhiza*, *Moschus berezovskii*	Tonify qi, activate blood, dispel stasis, relieve pain, and dilate vessels	[92]

A second recurrent theme is redox-inflammasome coupling. In steatohepatitis models, activation of Nrf2-associated antioxidant defenses has been linked to reduced ROS burden and downstream inhibition of NLRP3 inflammasome signaling and pyroptosis (e.g., Danshen-Zexie Decoction) [81]. Autophagy-centered regulation has also been reported as another entry point into inflammatory control, where restoration of autophagy is associated with inhibition of NLRP3 activation and improvement of lipid accumulation and hepatic injury (e.g., Chaize Decoction) [82]. Additional formulations report improvements in lipid profiles, oxidative stress, and inflammatory infiltration in NAFLD settings (e.g., Jianpi Huoxue Formula), while network-based and in vivo studies suggest broader multi-target regulation spanning lipid metabolism, inflammation, and insulin resistance with corresponding phenotypic improvements (e.g., PingTang No. 5 Capsule) [83] [84].

Beyond fatty liver disease, Alisma also appears in dyslipidemia-oriented formula contexts. Network pharmacology and docking analyses of the Crataegus pinnatifida leaf-Alisma pairing implicate interactions with hyperlipidemia-relevant metabolic and inflammatory targets [85]. Overall, evidence across these formulations highlights shared pathway motifs that align with improvements in steatosis and hepatic inflammation, while individual prescriptions appear to intervene at different points along the gut-liver, oxidative-stress, inflammasome, and autophagy axes.

5.2. Alisma *orientale*-Containing Formulas in Renal Injury and Hyperuricemia-Related Pathology

Across hyperuricemia-associated nephropathy and fibrosis-oriented renal injury models, Alisma orientale-containing formulas show convergent renoprotective effects that map onto two recurring mechanistic modules: suppression of inflammatory signaling centered on JAK2/STAT3, NLRP3 inflammasome, and NF-κB-related cascades, and modulation of gut-immune-kidney interactions. In hyperuricemia-induced renal injury, Fuling-Zexie Formula reduced uric acid burden, alleviated tubular injury, and improved renal function, accompanied by inhibition of JAK2/STAT3 phosphorylation and suppression of NLRP3 activation with reduced IL-1β maturation [86]. In adenine-induced renal fibrosis, Siling Decoction decreased tubular damage and collagen deposition while inhibiting the AKT/

IKKβ/NF-κB axis, including reduced AKT and IKKβ phosphorylation and diminished NF-κB nuclear translocation [87]. Beyond renal injury models, a modified Zexie Decoction was reported to regulate early hypertension with phlegm-dampness characteristics through a gut-immune-kidney axis mechanism, including microbiota remodeling, improvement of mucosal immune markers, and attenuation of renal inflammation, with accompanying blood-pressure improvement [88].

Overall, available studies indicate that Alisma orientale-containing formulas mitigate renal inflammatory and fibrotic injury primarily by restraining JAK2/STAT3-, NLRP3-, and NF-κB-linked pathways, with additional contributions from gut-immune-kidney axis regulation in selected models.

5.3. *Alisma orientale*-Containing Formulas in Cardiovascular, Cerebrovascular and Neurological Disorders

Beyond metabolic indications, Alisma orientale-containing formulas have been reported to act in vascular and neuro-related models, with recurrent mechanisms involving modulation of platelet/thrombus formation, regulation of apoptosis-related pathways, and anti-inflammatory or antiviral effects in selected contexts. Network analysis of Zexie Decoction predicted targets relevant to dizziness and pathways linked to vascular tone and neuroinflammation [93]. In experimental thrombosis-related models, an optimized formula containing Scutellaria baicalensis, Alisma orientale, and Atractylodes japonica showed marked antiplatelet and antithrombotic activity, including inhibition of platelet aggregation and thrombus formation [71]. In nervous-system models, LW-AF derived from Liuwei Dihuang Decoction alleviated streptozotocin-induced LTP impairment and improved synaptic plasticity in a diabetes-related cognitive dysfunction setting [91], while another Alisma orientale-containing formulation reduced neuronal apoptosis and shifted Bcl-2/Bax signaling in cerebral ischemia-reperfusion injury models [92]. In addition, Qi Pi Pill exhibited anti-influenza activity with reduced viral infection and associated inflammatory responses [90].

Overall, available evidence suggests that Alisma orientale-containing prescriptions can influence vascular and neuroimmune outcomes through antiplatelet/antithrombotic actions, apoptosis regulation in neural injury models, and antiviral activity in specific respiratory infection models.

6. Conclusion and Future Directions

Research on *Alisma orientale* has expanded substantially over the past decade, revealing a medicinal plant whose biological complexity mirrors the diversity of its therapeutic applications. Advances in germplasm characterization—from chloroplast genomics and phylogenetic markers to authentication assays and G × E stability analyses—have established a reliable molecular and ecological framework for understanding the species' genetic diversity and quality variation. These foundational insights underscore that the pharmacological reliability of *A. orientale* depends on both precise molecular identification and careful management of eco-

logical variables such as soil microbiota, light intensity, hydrological conditions, and environmental contaminants. Together, these studies illustrate that *A. orientale* is not a chemically static entity but a plant whose metabolic output is tightly shaped by developmental, environmental, and evolutionary factors.

The phytochemical landscape of *A. orientale* continues to unfold, with protostane-type triterpenoids and alisol derivatives remaining the dominant bioactive signatures. Parallel discoveries of sesquiterpenes, lignans, alkaloids, phenolics, polysaccharides, and lectins enrich the understanding of this species' metabolic breadth. The integration of NMR, LC-MS/MS, HPTLC-bioautography, proteomics, and chemometric tools has accelerated the structural elucidation of new compounds, clarified their biosynthetic origins, and supported the development of quantitative markers for quality control. Multilevel analyses—spanning key enzymes such as HMGR and squalene epoxidases, jasmonate-responsive transcript and microRNA networks, and MeJA-induced proteomic shifts—demonstrate that triterpene accumulation is governed by a sophisticated regulatory architecture that connects environmental cues with metabolite biosynthesis.

Pharmacological investigations position *A. orientale* as a multi-system botanical agent with particularly strong activity in metabolic, inflammatory, hepatobiliary, renal, cardiovascular, ocular, and neurological disorders. Mechanistic studies converge on several central pathways—including PPARα, FXR, YAP/TAZ, JAK2/STAT3, TLR4/NF-κB, NLRP3, and Nrf2—that together explain the herb's broad protective properties. Complementing single-herb studies, multi-herb formulas containing *A. orientale* extend these benefits in clinically relevant disease models, supporting improved lipid handling, attenuated fibrosis, strengthened renal defense, enhanced neuroprotection, and antiplatelet effects. These formula-based insights indicate that *A. orientale* functions synergistically within traditional decoctions, providing both mechanistic depth and translational potential.

Although significant advances have been made in recent years, important limitations remain in the current body of research on *A. orientale*. First, the majority of mechanistic and efficacy studies remain confined to in vitro systems and animal models, with relatively limited validation in well-designed clinical studies. While these preclinical findings provide valuable insights into metabolic, inflammatory, hepatic, renal, and cardiovascular regulation, their direct translatability to human physiology and disease contexts remains uncertain. Second, although *A. orientale* is widely used in traditional prescriptions and shows promising effects in multi-herb formulations, clinical evidence is often indirect, heterogeneous in design, or embedded within complex formulas, making it difficult to attribute observed therapeutic outcomes specifically to *A. orientale* or its constituent compounds. Third, network pharmacology has been extensively applied to predict targets, pathways, and disease associations; however, many of these predictions rely on in silico inference and database-driven associations that may overestimate biological relevance without rigorous experimental validation. Discrepancies between predicted targets and experimentally confirmed mechanisms underscore the need for cau-

tious interpretation and targeted verification. Finally, issues related to dose-effect relationships, pharmacokinetics, long-term safety, and quality consistency across different germplasm and cultivation conditions remain insufficiently addressed. Accordingly, we emphasize that translation of in vitro observations to in vivo efficacy is currently constrained by the scarcity of exposure (PK/ADME) data, and that systematic ADME profiling and tissue-distribution studies of representative bioactive constituents are needed. Addressing these limitations through integrated clinical research, standardized material control, and mechanism-focused validation will be essential for advancing *A. orientale* from a traditionally valued medicinal herb toward evidence-based therapeutic application.

Despite these achievements, several avenues remain open for future exploration. First, a unified *A. orientale* germplasm database integrating genetic, chemical, ecological, and phenotypic data would greatly enhance breeding programs and standardization. Second, genome sequencing and functional genomics—including CRISPR-based validation of candidate triterpene biosynthetic genes—are needed to dissect pathway regulation with higher precision. Third, controlled cultivation systems that manipulate light, nutrient flows, and rhizosphere microbiota may enable rational tuning of medicinal compound profiles. Fourth, systematic pharmacokinetic, metabolomic, and toxicological studies are required to translate mechanistic findings into clinically grounded dosage strategies. Fifth, systematic investigations into changes in chemical composition and pharmacological synergy following the compatibility of *A. orientale* with Atractylodes macrocephala remain lacking. Finally, greater integration of network pharmacology, organoid models, single-cell profiling, and multi-omics approaches will help unravel how complex mixtures of *A. orientale* constituents interact with human physiological networks.

In sum, *Alisma orientale* stands at a productive intersection of phytochemistry, plant biology, and pharmacology. Continued interdisciplinary investigation promises not only to deepen the scientific understanding of this classical medicinal plant but also to support its modernization as a standardized, mechanism-based therapeutic resource in metabolic and inflammatory disease management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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