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Review Article

Grass Jelly Species (*Platostoma palustre*, *Premna trichostoma*, and *Cyclea barbata*): Phytochemistry, Pharmacology, and Translational Potential—A Review

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ABSTRACT

Grass jelly, a traditional Southeast Asian dessert, comes from three plants: *Platostoma palustre*, *Premna trichostoma*, and *Cyclea barbata*. Despite over a century of lab studies, no clinical therapeutic use exists. Recent genomics identified 1,228 metabolites in *P. palustre* and key flavonoid/polysaccharide pathways, but most compounds remain uncharacterized. Preclinical data show antioxidant (IC_{50} = 2.512 ppm), antidiabetic (37.1% glucose reduction), antihypertensive (36.25% ACE inhibition), and anticancer (57% tumor reduction) effects—yet nearly all studies use crude extracts or multi-herb mixes, making it impossible to attribute benefits specifically to grass jelly. Veterinary uses include improved sperm cryopreservation (80% vs. 63.3% conception) and 43.7% lower ammonia in poultry waste, but again with mixed formulations. Only one registered clinical trial exists (NCT02875275), and none tests grass jelly as a drug. We identify seven systemic gaps (e.g., extract-based research, attribution confusion, missing pharmacokinetics) and propose a five-phase framework to shift from descriptive work to mechanistic pharmacology—aiming to turn grass jelly into a model for phytochemical discovery and real-world application.

1. INTRODUCTION

Across Southeast Asia, the term "grass jelly" refers to a gelatinous dessert produced from at least three distinct plant species belonging to two different families, reflecting a remarkable case of convergent cultural selection. Known as *cincau* in Indonesia, *xiancao* (仙草, literally "herb of the immortals") in China, *hsian-tsao* in Taiwan, and *chao kuay* in Thailand, this traditional food has been consumed for generations as a refreshing treat and folk medicine (Sasmita and Ling 2017). The etymology—particularly the Chinese designation "herb of the immortals"—reflects the cultural perception of grass jelly as possessing quasi-medicinal properties, capable of cooling the body and treating various ailments. This dual role as both food and medicine positions grass jelly within the framework of functional foods, a category of increasing scientific and commercial interest that has attracted substantial research investment in recent decades.

The convergent selection of multiple unrelated species for similar applications raises intriguing ethnobotanical questions that extend beyond mere historical curiosity. What biochemical properties do these phylogenetically distant plants share that led diverse cultures to independently recognize their value? The answer likely lies in two key

characteristics that together create the unique properties of grass jelly. First, the presence of gel-forming polysaccharides that enable the characteristic gelatinous texture, which traditional communities learned to extract and manipulate through sophisticated processing techniques. Second, the accumulation of bioactive compounds—particularly phenolic compounds in the Lamiaceae species and alkaloids in *C. barbata*—that confer health-promoting properties and likely contributed to the plants' reputation as medicinal agents. Understanding the biochemical and genetic basis of this convergence can inform both drug discovery and sustainable agriculture, offering a model system for investigating how traditional knowledge can guide modern scientific inquiry.

Despite sharing a common culinary application, grass jelly is produced from at least three distinct plant species, and correct taxonomic identification is essential for interpreting the scientific literature. The plant, historically known as *Mesona chinensis* or *Mesona palustris* is now accepted as *Platostoma palustre* (Blume) A.J.Paton, belonging to the Lamiaceae family (Paton 1997). Similarly, *Premna oblongifolia* Merr. is now accepted as *Premna trichostoma* Miq. (de Kok 2013). *Cyclea barbata* Miers remains the accepted name for creeping grass jelly, belonging to the Menispermaceae family (Guinaudeau et al. 1993). This taxonomic clarification is essential for correct interpretation of scientific literature and ensuring reproducibility in future research, as many older studies use the former nomenclature. Throughout this review, we consistently use accepted taxonomic names, though we note that many cited studies use older nomenclature, and we have indicated these equivalences where relevant.

Traditional records indicate that *P. palustre* possesses a sweet and mild flavor and a cold nature, with medicinal effects encompassing clearing heat and dampness, cooling blood to alleviate heatstroke, quenching thirst, promoting diuresis, and eliminating heat and toxins (Tang et al. 2026). Pharmacological research has revealed that *P. palustre* contains flavonoids, phenolic acids, polysaccharides, and other chemical constituents, exhibiting various physiological activities including antioxidant, anti-hepatic injury, hypolipidemic, anti-inflammatory, antibacterial, and antiviral effects (Tang et al. 2026). In many East and Southeast Asian countries, grass jelly has been used in folk medicine to treat various conditions, with traditional medicine practitioners and researchers commonly attributing antioxidant, antitumor, anti-inflammatory, and antihypertensive properties to these preparations.

A review by Sasmita and Ling (2017) highlighted the plant's pre-clinical potential as a nutraceutical agent, noting its antioxidative, anti-inflammatory, anti-hypertensive, and immunomodulatory properties, while explicitly stating that more thorough characterization, pharmacological, and molecular studies should be conducted not only to avoid adverse risks but also to properly direct its use as a nutraceutical agent for specific indications. This sentiment has been echoed by subsequent reviews, with Rahmah et al. (2022) concluding that the application of the effectiveness of *M. palustris* in humans still needs to be developed. Despite a growing body of scientific investigation spanning over a century, the translational potential of these species remains unrealized. In our assessment of the literature, we were particularly struck by the disconnect between the extensive preclinical evidence and the complete absence of clinical translation. This gap, in our view, reflects not merely scientific limitations but also systemic deficiencies in how natural product research is conducted and translated. Our review aims to systematically identify the barriers to translation and propose concrete pathways forward.

This review provides the first comprehensive comparative analysis of the three principal grass jelly species, encompassing taxonomic clarification, genomic characterization, phytochemical profiling, pharmacological activities, clinical translation status, material science applications, veterinary applications, and agronomic considerations. We critically assess the evidence base, identify systemic deficiencies that perpetuate their status as promising but unvalidated botanical resources, and propose a transformative research framework to transition grass jelly research from descriptive extractology to mechanistic pharmacology.

We conducted a comprehensive literature search across PubMed, Scopus, Web of Science, and Google Scholar, using search terms including "*Platostoma palustre*," "*Mesona palustris*," "*Premna trichostoma*," "*Premna oblongifolia*," "*Cyclea barbata*," "grass jelly," "cincau," "hsian-tsao," and "xiancao." We included English-language and Indonesian-language publications, with no restriction on publication date. We also searched ClinicalTrials.gov for registered clinical trials. While we aimed for comprehensiveness, this review is narrative rather than a formal systematic review with a registered protocol; however, our search strategy was systematic in its coverage of the major databases and key terms, and we have attempted to trace all claims back to primary sources where possible. In cases where claims could only be verified through review articles, we have explicitly noted this limitation.

2. TAXONOMY AND BOTANICAL CHARACTERIZATION

2.1. The Taxonomic Landscape

The term "cincau" in Indonesian encompasses a remarkable diversity of plant species, reflecting the cultural importance of these plants across the archipelago. In Indonesia alone, at least five distinct types are recognized: *cincau hitam* (black grass jelly), *cincau hijau rambat* (creeping green grass jelly), *cincau perdu* (shrub grass jelly), *cincau jelly*, and *cincau minyak*. The most widely utilized species are the three that form the focus of this review: *Platostoma palustre* (*cincau hitam*), *Premna trichostoma* (*cincau perdu*), and *Cyclea barbata* (*cincau rambat*). These three species represent two distinct plant families—Lamiaceae and Menispermaceae—and their phylogenetic

distance explains fundamental differences in their phytochemical profiles and pharmacological activities.

The Lamiaceae family, to which both *P. palustre* and *P. trichostoma* belong, is one of the largest plant families, comprising approximately 9,743 species globally. Members of this family are characterized by opposite leaves, square stems, bilabiate flowers, and production of essential oils, phenolic compounds, flavonoids, and terpenes. In contrast, *Cyclea barbata* belongs to the Menispermaceae family (order Ranunculales), a family renowned for producing diverse alkaloids, particularly bisbenzylisoquinoline alkaloids. This phylogenetic distance is reflected in the markedly different phytochemical profiles of these species, with *C. barbata* accumulating alkaloids at concentrations that are remarkably high for plant material (up to 7% by weight in roots). A comparative summary of the three species' taxonomic characteristics, traditional uses, and key phytochemical features is provided in **Table 1.**

2.2. Phylogeny and Cytogenetics

Recent advances in cytogenetic analyses have provided deeper insights into the genetic diversity and evolutionary relationships within *Platostoma palustre*. Zhao et al. (2025) conducted comprehensive cytotype classification and genetic diversity analysis using rDNA localization and chloroplast genome sequencing, revealing significant intraspecific variation with the identification of three distinct cytotypes: diploid (2n = 2x = 30), triploid (2n = 3x = 45), and tetraploid (2n = 4x = 60). This polyploid series suggests that polyploidization events may have contributed to the adaptive radiation and domestication of this species across different geographical regions. The chloroplast genomes of *P. palustre* accessions maintained a conserved single circular molecule with a length of 152,534–152,788 bp, and phylogenetic analysis showed that most accessions clustered according to their collection regions, indicating geographic structure in the genetic diversity that may have implications for breeding programs.

For related species, the complete chloroplast genome of *Cyclea hypoglauca* (Schauer) Diels, 1910 has been characterized as 159,596 bp in length with 129 genes (Mach et al. 2026). Additionally, the chloroplast genome of *Premna obtusifolia* has been assembled as 153,415 bp (Wang 2025), and phylogenetic studies on *Premna* in Thailand using four chloroplast regions (*ndhF*, *rbcL*, *rps16*, and *trnL-F*) have provided insights into the *P. serratifolia* complex (Satthaphorn et al. 2025). These genomic resources provide valuable tools for species identification and phylogenetic studies, though the lack of similar resources for *P. trichostoma* and *C. barbata* represents a significant gap that requires urgent attention.

Table 1. Comparative summary of the three principal grass jelly species.

Characteristic	*Platostoma palustre*	*Premna trichostoma*	*Cyclea barbata*
Family	Lamiaceae	Lamiaceae	Menispermaceae
Common names	Black grass jelly, *cincau hitam*, *xiancao*	Shrub grass jelly, *cincau perdu*	Creeping grass jelly, *cincau rambat*
Growth form	Herbaceous	Shrub	Creeping vine
Ploidy	Diploid (2n=30), triploid (45), tetraploid (60)	Not characterized*	Not characterized*
Traditional preparation	Dried leaves/stems boiled with alkaline ash; starch added	Fresh leaves crushed in water; natural gelation	Fresh leaves crushed in water; natural gelation
Gelation mechanism	Alkaline extraction + starch addition	Endogenous PME† + calcium cross-linking	Endogenous PME† + calcium cross-linking
Key phytochemicals	Phenolic acids, flavonoids, polysaccharides, terpenes	Chlorophyll, flavonoids, pectin	Bisbenzylisoquinoline alkaloids, flavonoids
Major pharmacological activities	Antioxidant, immunomodulatory, antidiabetic, anticancer	Antioxidant, hypocholesterolemic	Antioxidant, anti-inflammatory, immunomodulatory
Veterinary applications	Sperm cryopreservation, ammonia reduction	None reported	None reported
Genome size	~1.21 Gb	Not characterized*	Not characterized*
Chloroplast genome	152,534–152,788 bp	Not characterized*	Not characterized*

*The lack of genomic characterization for *P. trichostoma* and *C. barbata* represents a significant gap in the literature that requires urgent attention.
†PME: pectin methyl esterase

Source: Compiled from Paton (1997), de Kok (2013), Guinaudeau et al. (1993), Zhao et al. (2025), Li et al. (2022), Tang et al. (2023), Wei et al. (2025), Yuliarti et al. (2017), Arkarapanthu et al. (2005), Lin et al. (1993), Dianita and Jantan (2017), Fildzah et al. (2025).

2.3. Genetic Diversity and Domestication

Li et al. (2022) conducted genome survey sequencing of *P. palustre* and developed simple sequence repeat molecular markers, revealing an assembled genome size of approximately 1.21 Gb. A total of 15,498 SSR motifs were identified, with dinucleotide repeats being the most abundant (68.3%). Phylogenetic analysis using these markers successfully distinguished 12 clones of *P. palustre* and related species into subgroups, demonstrating the utility of these markers for cultivar identification and breeding programs. Li et al. (2026b) further developed 15 pairs of polymorphic SSR primers with polymorphism information ranging from 0.197 to 0.736, enabling comprehensive genetic diversity analysis of 40 germplasms, providing a foundation for conservation and breeding efforts.

You et al. (2024) conducted integrated metabolomic and transcriptomic analyses of flavonoid accumulation in different cultivars of *P. palustre*, comparing the Taiwan and Pingyuan cultivars widely grown in Guangdong. The study revealed that the Taiwan cultivar exhibited greater leaf area, more non-glandular hairs, and a higher number of stomata than the Pingyuan cultivar, and also exhibited higher total flavonoid content and antioxidant activity. Transcriptome analysis identified 2,503 differentially expressed genes primarily involved in amino acid metabolism, carbohydrate metabolism, sorting, and degradation, with bHLH and MYB being the top two most abundant transcription factor families. Combined analysis indicated that the phenylpropanoid pathway plays a significant role in flavonoid synthesis, providing targets for metabolic engineering. These findings suggest that cultivar selection could be a powerful tool for optimizing bioactive compound content in grass jelly products.

2.4. Functional Genomics of Bioactive Compound Biosynthesis

Chen et al. (2024) performed genome-wide identification and expression analysis of the WRKY gene family in *P. palustre*, identifying 133 PpWRKY gene family members unevenly distributed on 15 chromosomes. Segmental duplication events played a crucial role in the expansion of this gene family, and expression profiles revealed that PpWRKY genes respond to cadmium, red light, salt, and drought stresses, with PpWRKY92 exhibiting simultaneous responses to multiple abiotic stresses. Furthermore, several PpWRKY genes demonstrated strong correlations with both monosaccharides and flavonoids, suggesting their involvement in regulating bioactive compound biosynthesis and providing potential targets for enhancing production of valuable metabolites through genetic engineering or breeding programs.

Quan et al. (2026) employed integrated transcriptomics and weighted gene co-expression network analysis to elucidate the biosynthesis and regulatory mechanisms of flavonoids in *P. palustre*, identifying seven key enzyme genes involved in flavonoid biosynthesis, including UDP-glucose flavonoid 3-O-glucosyltransferase, flavonoid 3′-monooxygenase, flavonol synthase, and flavonoid 3′,5′-methyltransferase. Multiple key hub transcription factors belonging to bHLH, TCP, AUX/IAA, AP2/ERF, HB-KNOX, and GATA families were identified as potential regulators of flavonoid biosynthesis. Wei et al. (2025) employed multi-omics analysis to reveal key genes involved in polysaccharide biosynthesis induced by red light intensity in *P. palustre*, identifying critical regulatory nodes in the polysaccharide biosynthetic pathway. This work, together with studies on cadmium stress (Wei et al. 2026), salt stress (Quan et al. 2025), and high-temperature stress (Li et al. 2025), demonstrates the remarkable capacity of *P. palustre* to modulate its secondary metabolite profile in response to environmental stimuli. In practice, this means that cultivation conditions can be optimized to enhance the production of specific bioactive compounds, a finding with significant implications for commercial production.

2.5. DNA Barcoding for Species Identification and Quality Control

Thummajitsakul and Silprasit (2020) developed a short ITS DNA barcode (277 nucleotides) for effective identification of *C. barbata*, distinguishing it from adulterants such as *Cissampelos pareira*, *Cyclea polypetala*, and *Stephania japonica*. The study demonstrated that the short ITS region was able to distinguish *C. barbata* from its adulterants, reducing cost and time for identification using DNA barcode technology. This tool is particularly valuable for quality control in commercial grass jelly production, where adulteration with morphologically similar but chemically distinct species could affect product quality and safety. The application of DNA barcoding as a routine quality control measure in the grass jelly industry could help ensure product authenticity and consistency, protecting both consumers and producers. In our view, this represents an underutilized opportunity for quality assurance that should be more widely adopted.

3. TRADITIONAL PREPARATION AND GELATION MECHANISMS

3.1. Traditional Preparation Methods

The preparation of grass jelly differs substantially between species, reflecting their distinct biochemical properties and the traditional knowledge that developed around each species. Green grass jelly, derived from *Cyclea barbata* and *Premna trichostoma*, is prepared by crushing or kneading fresh leaves in water until the mucilage and green pigments are released. The mixture is then filtered, and the resulting liquid is left to set at room temperature. This process relies on the natural gelation of pectin, facilitated by endogenous pectin methyl esterase enzymes and divalent cations (particularly calcium) present in the leaf material (Yuliarti et al. 2017; Arkarapanthu et al. 2005). No additional ingredients are required, making green grass jelly a remarkably "clean-label" product that exemplifies sophisticated traditional food processing techniques developed without modern food additives. The simplicity of this process—requiring only leaves and water—

suggests that early practitioners may have discovered the gelation properties through observation of leaf macerates setting naturally, representing an early example of food biotechnology.

Black grass jelly, derived from *Platostoma palustre*, requires a more complex process that reflects the different biochemical properties of this species. The leaves and stems must first be dried until they turn dark brown to black, a process that likely concentrates the gel-forming polysaccharides and initiates chemical changes. The dried material is then boiled with water, traditionally with the addition of ash from rice husks (*abu merang*), which provides alkaline conditions and minerals that facilitate gelation. The resulting dark liquid is filtered, and starch (such as tapioca) is often added to achieve the desired firm texture. This traditional processing technique, which involves alkaline extraction and starch addition, is more complex than green grass jelly preparation and likely evolved to extract the gel-forming polysaccharides that are less readily released by simple crushing. The molecular basis for this difference lies in the structural properties of *P. palustre* polysaccharides, which are less readily solubilized by simple aqueous extraction and require alkaline conditions to disrupt intermolecular associations and release the gel-forming polymers (Tang et al. 2023; Wei et al. 2025). The cultural and geographic distributions of the three species—with *P. palustre* being more widely cultivated in China and Taiwan, *C. barbata* in Indonesia and Malaysia, and *P. trichostoma* in specific regions of Indonesia—reflect local adaptations to available plant resources and the development of regionally specific processing traditions.

Product diversification has expanded the traditional repertoire, creating new commercial opportunities. An innovative product, *nata de cincau*, has been developed from black cincau (*Mesona palustris*) in Pacitan, Indonesia (Naja et al. 2019). The study optimized the formulation of *nata de cincau* with 12.5% substrate concentration and 15% starter concentration, which was found to be the best formulation based on physical, chemical, and sensory characteristics. This diversification of black cincau products represents an important step in value addition and commercialization of grass jelly resources, creating new markets and income opportunities. Patents related to grass jelly products have been filed, including Indonesian Patent P00201201150: "Cincau Hitam Seduh dan Proses Pembuatannya" (Brewed Black Cincau and Its Manufacturing Process) and P00201201111: "Formula Nutrisi Tambahan Yang Mengandung Cincau Hitam (*Mesona palustris*) dan Proses Pembuatannya" (Additional Nutritional Formula Containing Black Cincau and Its Manufacturing Process), indicating commercial interest in these products (Frediansyah et al. 2012a; Frediansyah et al. 2012b).

3.2. Gelation Mechanisms

The gelation properties of grass jelly species have been the subject of significant scientific investigation, revealing sophisticated biochemical mechanisms that traditional communities have exploited for generations. Yuliarti et al. (2017) extensively characterized the polysaccharide fraction from *C. barbata*, revealing that the gelation mechanism involves two critical steps: first, the action of pectin methyl esterase de-esterifies highly esterified pectin (DE up to 97%) to a low-methoxyl form (DE ~10%); second, divalent cations (primarily calcium) mediate cross-linking between adjacent galacturonic acid chains. The isolated pectin has a weight-average molecular weight of approximately 4.4×10^5 g/mol and consists primarily of galacturonic acid (~35.8% w/w) and neutral sugars (~6.8% w/w) (Yuliarti et al. 2017). This mechanism explains why cold-water extraction of *C. barbata* leaves yields a gel at room temperature without requiring added sugars or acids. The endogenous enzyme pectin methyl esterase is activated during crushing, de-esterifying the pectin and allowing calcium-mediated cross-linking, a mechanism that represents an elegant example of enzyme-assisted food processing.

Arkarapanthu et al. (2005) reported that the polymer is polygalacturonic acid of average molecular weight 741 kDa with 66.3% methylation. Yuliarti and Mardyiah Binte Othman (2018) further investigated the temperature dependence of acid- and calcium-induced gelation of low-methoxyl pectin extracted from *C. barbata*, revealing that gelation is influenced by temperature, pH, and calcium concentration. Gels formed at higher temperatures exhibited lower gel strength, while acid-induced gels showed different rheological properties compared to calcium-induced gels. The addition of NaCl enhanced gel structure through electrostatic screening effects. These findings have important implications for optimizing grass jelly processing and developing novel food products with tailored texture and stability, enabling manufacturers to fine-tune gel properties for specific applications. For *P. trichostoma*, Elsyana and Alvita (2021) characterized the pectin, revealing an equivalent weight of 1162.72 mg, methoxyl content of 5.06%, galacturonic acid content of 59.84%, and degree of esterification of 48.01%, classifying it as low-methoxyl pectin.

For *Premna microphylla*, a related species that shares gelation properties, Liu et al. (2026) demonstrated that extraction methods significantly impact pectin properties, with yields ranging from 12.59% to 17.53% and galacturonic acid content from 70.30% to 76.43%. Rheological tests revealed that hot water-extracted pectin had the highest apparent viscosity and thixotropy, likely due to its higher Ca^{2+} content. Fei et al. (2025) further elucidated the calcium-induced gelation mechanism of *P. microphylla* polysaccharide, showing that electrostatic interactions played a crucial role in gel formation. Zhu et al. (2026) compared pectic polysaccharides from *Premna microphylla* and *Abelia macrotera*, revealing that the linear architecture of *P. microphylla* pectin (molecular weight 1258.83 kDa, DM 30.97%, HG content 73.97%) facilitated the construction of a dense and ordered network, resulting in superior rheological properties, textural hardness, freeze-thaw stability, and thermal stability. These findings suggest that

Premna species may offer advantages for certain industrial applications requiring stable gel structures.

3.3. Extraction Optimization

Extraction optimization studies using response surface methodology have been conducted to maximize the yield of antioxidant phenolic compounds from black grass jelly (*Mesona palustris*). Optimal extraction conditions occurred at a temperature range of 94–100°C with a solvent ratio of 23–24 ml/g (Hendratama et al. 2020). Additionally, pilot plant scale extraction using historical-data response surface methodology demonstrated that the optimum extraction process was achieved at 153.65 minutes (2.5 hours) with predicted values of total phenolic compounds (1.636 ± 0.12 mg CAE/g), antioxidant activity (49.57 ± 12.26%), and extraction cost (IDR 1.733 million), confirming the feasibility of commercial-scale extraction (Widyaningsih et al. 2018). These optimization studies provide a foundation for industrial-scale production of grass jelly extracts for nutraceutical applications, though further work is needed to optimize for specific bioactive compounds rather than total phenolic content. In our assessment, this represents a significant opportunity for process optimization that could improve both yield and product consistency.

4. PHYTOCHEMICAL PROFILES

4.1. *Platostoma palustre* (Black Grass Jelly)

The phytochemical profile of *P. palustre* is the most extensively characterized among the three species, largely due to recent advances in metabolomic technologies that have enabled comprehensive profiling. Huang et al. (2024) conducted a comprehensive widely targeted metabolomic analysis of *P. palustre* stems and leaves at different growth stages, detecting 1,228 metabolites across multiple classes. This remarkable chemical diversity includes 241 phenolic acids, 203 flavonoids, 152 lipids, 128 terpenes, 106 amino acids, 79 organic acids, 74 saccharides, 66 alkaloids, and 44 lignans, revealing *P. palustre* as a rich source of diverse bioactive compounds. However, we must emphasize that most of these metabolites are present in trace amounts and may not be pharmacologically relevant; the presence of a compound does not necessarily indicate bioactivity, and careful prioritization is needed to identify compounds with genuine therapeutic potential. This distinction is crucial: the metabolomic profile provides a starting point for investigation, not a validated pharmacopoeia.

KEGG enrichment analysis revealed that arginine biosynthesis was the common differential metabolic pathway in different growth stages and tissues, suggesting that nitrogen metabolism may be particularly important for the plant's development and secondary metabolite production. The volatile constituents of *P. palustre* have been characterized by Kung et al. (2019) using headspace solid-phase microextraction and simultaneous distillation-extraction. The study identified 120 volatile components, with HS-SPME identifying 56 components (mainly α-pinene, β-pinene, and limonene) and SDE identifying 108 components (mainly α-bisabolol, β-caryophyllene, and caryophyllene oxide). Nongshi No. 1 had the highest total quantity of volatile components using HS-SPME, while Taoyuan Mesona 1301 showed the highest volatile concentration using SDE, indicating significant cultivar-dependent variation in volatile profiles. Zhong et al. (2024) further investigated volatilome and flavor profiles across different ploidy germplasms, identifying sixty-seven volatile compounds across ten classes, with six volatile compounds screened as potential marker compounds to discriminate stems and leaves.

The proximate composition of dried leaves includes protein (4.6–10.04%), fat (0.1–0.9%), fiber (1.07–2.98%), and ash (26.2–30.9%) (Rahmah et al. 2022). The phenolic profile is dominated by rosmarinic acid (46.96 μg/mL) and caffeic acid (29.29 μg/mL) as the major compounds (Liu et al. 2023). Water extraction of *M. palustris* resulted in pure extracts amounting up to 45% yield with a total phenol content of 170.33 mg/g (Sasmita and Ling 2017). Deswati et al. (2024) reported that all fractions exhibited $IC_{50} < 50$ ppm, categorizing them as having "very high" antioxidant activity, with the ethyl acetate fraction demonstrating the most potent activity. We address the interpretation of these IC_{50} values in Section 5.1, as the extraordinarily low values raise concerns about assay interference.

Polysaccharides are the main functional component of *M. chinensis* (Seah et al. 2024a; Seah et al. 2024b), with structural heteropolysaccharides composed of α-1,4-linked galacturonan backbone with some α-1,2-linked rhamnose residues, and large amounts of uronic acid. Pan et al. (2024) provided a comprehensive review of the preparation technologies, structural features, and biological activities of polysaccharides from *Mesona chinensis* Benth., highlighting their diverse health-promoting effects including immunomodulatory, antioxidant, and prebiotic activities. Tang et al. (2023) compared the effects of different processing methods on the metabolites and volatile substances of *P. palustre*, finding that the sweating treatment promoted the accumulation of total sugar, soluble sugar, and total pectin compared to tedding and drying treatments but decreased total flavonoid contents. These findings have important implications for post-harvest processing, as the choice of processing method significantly affects the final chemical composition and potentially the bioactivity of the product.

Huang et al. (2024b) compared organic and compound fertilizer effects on *P. palustre* yield and metabolites, finding that both compound fertilizer and organic fertilizer promoted fresh weight, shade dry weight, and dry weight, with metabolomic analysis revealing 1,096 metabolites and the flavone and flavonol biosynthesis pathway being the most significantly differential metabolic pathway between treatments. Chen et al. (2024b) investigated the effects of different colors of plastic-film mulching on soil temperature, yield, and metabolites of *P. palustre*, with green film treatment

significantly increasing single plant fresh weight compared to white film treatment. These agronomic studies provide valuable guidance for optimizing cultivation practices to enhance both yield and bioactive compound content.

4.2. *Cyclea* barbata (Creeping Grass Jelly)

The Menispermaceae family is renowned for alkaloid production, and *C. barbata* exemplifies this trait with roots containing 4–7% alkaloids by weight (Lin et al. 1993). The principal alkaloid is (+)-*S,S*-tetrandrine, which can constitute up to 3% of the root material (Lin et al. 1993), representing an exceptionally high concentration for a bioactive compound in plant material. This high abundance makes tetrandrine an attractive candidate for isolation and development, as it can be obtained in sufficient quantities for research and potentially commercial applications.

Guinaudeau et al. (1993) isolated two new bisbenzylisoquinoline alkaloids, (−)-2′-norlimacine and (+)-cycleabarbatine, alongside known compounds including (+)-tetrandrine-2′-β-N-oxide, (+)-berbamine, (−)-repandine, (+)-cycleanorine, (+)-daphnandrine, (−)-curine, (+)-coclaurine, and (−)-*N*-methylcoclaurine. Lin et al. (1993) further identified five bisbenzylisoquinoline alkaloids—(+)-tetrandrine, (−)-limacine, (+)-thalrugosine, (+)-homoaromoline, and (−)-cycleapeltine—as the active principles responsible for cytotoxic and antimalarial activities, demonstrating the pharmacological potential of this alkaloid-rich species.

Studies on the neuromuscular blocking activity of alkaloids from *C. barbata* revealed that *l*-curine dimethiodide and dimethyl-*l*-curine dimethochloride demonstrated significant neuromuscular blocking activity, with the latter being approximately four times as powerful as *l*-curine and having 250–300 times higher water solubility (Tang et al. 1980a; Tang et al. 1980b). These findings have potential applications in anesthesia and neuromuscular disorders, though the toxicity profile would need careful evaluation. Wang et al. (2019) isolated two new azafluoranthene alkaloids and a new phytoecdysone from the stems of *C. barbata*, marking the first report of azafluoranthene alkaloids and phytoecdysones from the *Cyclea* genus, with four isolates showing moderate hepatoprotective activity against APAP-induced toxicity in HepG2 cells.

Noviyanti et al. (2020) confirmed the presence of coclaurine in *C. barbata* using LC-MS and demonstrated that coclaurine has the highest binding affinity to activate estrogen receptor α, suggesting potential applications in reproductive health. Thummajitsakul et al. (2019) found that the total phenolic content of old, fresh leaves was highest (525.08 mg gallic acid/g extract), while old, dry leaves exhibited the highest ABTS radical scavenging activity (97.7%). Secondary metabolites found in stems, roots, and leaves of *C. barbata* include alkaloids and flavonoids, and the pharmacological activities of *C. barbata* include antibacterial, antioxidant, anti-plasmodial, immunomodulator, anti-Alzheimer, anti-inflammatory, anti-cholesterol, and antiulcer effects (Fadhlurrahim et al. 2022).

4.3. *Premna trichostoma* (Shrub Grass Jelly)

The phytochemical profile of *Premna trichostoma* (formerly *P. oblongifolia*) is less comprehensively characterized than the other species, though recent studies have identified several key compounds. Dianita and Jantan (2017) noted that more than 250 compounds have been isolated from the genus *Premna*, comprising diterpenoids, iridoid glycosides, and flavonoids as the most common secondary metabolites, suggesting that this genus is a rich source of bioactive compounds awaiting further investigation. The species is exceptionally rich in chlorophyll, with concentrated ethanolic extracts containing 1184.475 mg/L total chlorophyll (Novelina et al. 2015). Fildzah et al. (2025) identified 28 bioactive compounds through GC-MS analysis, with the most abundant being phytol (19.06%), squalene (4.32%), Urs-12-en-28-oic acid derivatives (6.23%), and 8,11,14-Eicosatrienoic acid (2.88%). The ethanol extract of green cincau leaves demonstrated low cytotoxicity against rat bone marrow-derived mesenchymal stem cell-like cells, maintaining cell viability above 80% at all tested concentrations, and Alizarin Red S staining revealed calcium deposit formation at 300 μg/mL, suggesting preliminary osteogenic activity that warrants further investigation for bone health applications.

Elsyana and Alvita (2021) characterized the pectin from *P. trichostoma* leaves, revealing an equivalent weight of 1162.72 mg, methoxyl content of 5.06%, galacturonic acid content of 59.84%, and degree of esterification of 48.01%, classifying it as low-methoxyl pectin. Green *cincau perdu* extract contains pectin up to 19.7% and various phytochemicals, making it a potential source of dietary fiber with antioxidant properties. Salihu et al. (2024) reported on the essential oil components of *Premna trichostoma*, and Sulistiyanto et al. (2022) evaluated the effects of liquid organic and NPK fertilizers on the nutrient composition of *P. oblongifolia* grown in tropical peat soil, providing guidance for cultivation practices.

5. PHARMACOLOGICAL ACTIVITIES

5.1. Antioxidant Activity

The antioxidant activity of grass jelly species is extensively documented across multiple assays, laboratories, and solvent systems, representing the most widely studied pharmacological property of these plants. However, several critical caveats must be considered when interpreting these findings. First, the DPPH and ABTS assays are chemical assays that measure radical scavenging in solution, not biological antioxidant capacity in vivo. Second, colored compounds in plant extracts (particularly chlorophyll and flavonoids) can interfere with absorbance measurements, leading to artificially low IC_{50} values. Third, the relevance of in vitro radical scavenging to human health—where antioxidant effects depend on absorption, distribution, metabolism, and excretion—is increasingly questioned. Notably, no studies have employed more physiologically relevant assays such as cellular antioxidant activity (CAA) assays, which measure

antioxidant capacity in cell culture models, or in vivo measures of oxidative stress such as plasma malondialdehyde or F_2-isoprostane levels. We were particularly struck by this absence, as CAA assays would provide a more meaningful assessment of antioxidant potential in a biological context.

With these caveats, Deswati et al. (2024) conducted a comprehensive evaluation of *P. palustre* leaf extract and its fractions using ABTS, DPPH, and FRAP assays, with the ethyl acetate fraction demonstrating IC_{50} values of 2.512 ppm in ABTS, 17.74 ppm in DPPH, and reducing power of 20.24 mg AAE/g sample. We note that the ABTS IC_{50} of 2.512 ppm is extraordinarily low—approaching the range of pure reference compounds such as Trolox (IC_{50} ~2.5–3.0 μg/mL). This may reflect interference from colored compounds in the extract rather than genuine radical scavenging activity, or it may indicate that the dose-response curve was not adequately characterized. Future studies should employ CAA assays to confirm antioxidant activity and quantify the contribution of individual compounds. All fractions had IC_{50} < 50 ppm, categorizing them as having "very high" antioxidant activity, though these values should be interpreted with caution.

Lin et al. (2017) evaluated the antioxidant properties of *P. palustre* ethanolic extracts with different ethanol concentrations, finding that the 60% ethanolic extract exhibited higher total phenol content, total flavonoid content, DPPH and ABTS scavenging activities, and reducing power, along with the most significant protective effect against oxidative DNA damage and protection of Raw 264.7 mouse macrophages against H_2O_2-induced damage, with no cell toxicity up to 250 μg/mL. This study provides some evidence for cellular protection, though the concentration used were relatively high. Gangga et al. (2020) formulated antioxidant gel from standardized green cincau (*C. barbata*) ethanolic extract, with Formula II showing the strongest antioxidant activity (IC_{50} = 57.60 μg/mL) after 3 months of storage at 40°C, demonstrating the potential for stable formulation development.

For *P. trichostoma*, Novelina et al. (2015) reported an IC_{50} of 6533.9 ppm for chlorophyll extract, considerably higher than that of *P. palustre* and *C. barbata*, reflecting differences in the phenolic content and composition of the species. For *Premna serratifolia*, Hadiarti et al. (2026) reported that extracts from different geographic locations in West Kalimantan showed varying antioxidant activities, with PLS analysis revealing that C-H alkane, O-H, and isoferulic acid were the most influential compounds in determining antioxidant activity. **Table 2** summarizes antioxidant activities with evidence quality ratings, highlighting that all studies currently fall into the "low" evidence quality category due to reliance *in vitro* assays with crude extracts and the potential for assay interference.

Table 2. Summary of antioxidant activities with evidence quality ratings.

Species	Extract/Fraction	Assay	IC_{50}	Evidence Quality*	Limitation
P. palustre	Ethyl acetate fraction	ABTS	2.512 ppm	Low	Potential assay interference; single study
P. palustre	Ethyl acetate fraction	DPPH	17.74 ppm	Low	Potential assay interference; single study
C. barbata	Ethanolic extract	DPPH	57.60 μg/mL	Low	Crude extract; no compound identification
P. trichostoma	Chlorophyll extract	DPPH	6533.9 ppm	Low	Crude extract; limited relevance

*Evidence Quality: Low = In vitro only, crude extract, no compound identification; Moderate = In vitro with characterized fractions; High = Cellular or in vivo assays with characterized compounds.

Source: Deswati et al. (2024), Lin et al. (2017), Gangga et al. (2020), Novelina et al. (2015).

5.2. Immunomodulatory and Anti-inflammatory Activity

A critical methodological concern must be addressed upfront: several studies cited in this section use multi-herb formulations where grass jelly is combined with other ingredients. These studies cannot attribute observed effects specifically to grass jelly—a problem we refer to as the "attribution problem." Studies using multi-herb formulations provide only weak evidence for grass jelly activity and should be treated with caution. They are included here for completeness but are not considered strong evidence for the pharmacological activity of grass jelly alone. In our assessment, this is a pervasive issue in the literature that fundamentally undermines the evidence base for grass jelly's immunomodulatory effects.

In a study using a multi-herb formulation containing black cincau and red ginger, Widyaningsih et al. (2017) investigated immunomodulatory effects in *E. coli* O157-infected mice, demonstrating modulation of T-cell populations and $CD68^+$IFN-γ monocytes, along with recovery of intestinal mucosa structure. However, the presence of red ginger in the formulation confounds attribution of effects to black cincau alone. We therefore classify this as weak evidence, as the observed effects could be due entirely to red ginger or to synergistic interactions that would not occur with grass jelly alone. Similarly, Widyaningsih et al. (2020) examined a five-herb formulation (*wedang uwuh*) containing black cincau in alloxan-induced diabetic rats, with the formulation significantly modulating cytokine expression. The multi-herb formulation again limits attribution; we classify this as weak evidence.

In a study using a black cincau-based supplement (not a multi-herb formulation), Widyaningsih et al. (2018)

investigated the anti-inflammatory effect in carrageenan-induced mice, with both doses effectively inhibiting edema and reducing TNF-α and CD68 expression. This study provides stronger evidence, though it uses a crude extract rather than a characterized compound, limiting mechanistic understanding. Handayani et al. (2018) confirmed that the ethyl acetate extract of *C. barbata* had the highest lipoxygenase inhibiting activity with an IC_{50} value of 0.267 μg/mL, suggesting that *C. barbata* has potential as a natural anti-inflammatory agent. Yang et al. (2026) investigated the antioxidant, antibacterial, and anti-inflammatory activities of *Premna puberula* root bark extracts, identifying 48 compounds including 14 phenolic compounds and 6 flavonoids, with the aqueous extract significantly suppressing LPS-induced release of NO, TNF-α, and IL-6, and downregulating iNOS, COX-2, and proteins associated with NF-κB and MAPK signaling pathways.

Strength of Evidence Summary: While the immunomodulatory activity of black cincau is supported by studies using a single-ingredient formulation, the evidence from multi-herb formulations must be interpreted with caution due to the attribution problem. All studies use crude extracts rather than characterized compounds, limiting mechanistic understanding. We recommend that future studies use single-ingredient formulations only, employ bioactivity-guided fractionation to identify active compounds, and include both male and female animals to assess sex-specific effects.

5.3. Antidiabetic Activity

The antidiabetic potential of grass jelly species has been demonstrated in several in vivo studies. Studies on streptozotocin-induced diabetic rat models demonstrated that treatment with *M. palustris* extracts (54 mg/200 mg) combined with glibenclamide significantly reduced fasting blood glucose from 1.91 g/L to 0.795 g/L (a 37.1% reduction) and resulted in significantly higher pancreatic β-cell counts (primary study cited in Rahmah et al. 2022). This combination approach is clinically relevant, as many diabetic patients take multiple medications, and the potential for herb-drug interactions requires careful investigation. In vitro studies indicated that *M. chinensis* extract prevents AGE formation and protein oxidation against fructose-induced protein glycation in vitro (Seah et al. 2024a; Seah et al. 2024b), suggesting that the antidiabetic effects may involve multiple mechanisms, including both glucose-lowering effects and prevention of diabetic complications through inhibition of advanced glycation end-product formation.

A study by Lim et al. (2018) investigated the effects of grass jelly on glycemic control, demonstrating that hydrocolloids in grass jelly may inhibit gut carbohydrase activity and reduce glycaemic response. The study recruited 15 healthy Chinese men who consumed glucose solution, grass jelly solution with glucose, or grass jelly gel with glucose, representing one of the few studies that has directly examined the metabolic effects of grass jelly consumption in humans, albeit in a small sample. The findings suggest that the physical form of grass jelly (gel vs. solution) may affect glycemic response, with implications for product formulation. For *Premna serratifolia*, Bhayye et al. (2026) evaluated α-glucosidase inhibition potential, identifying six compounds as putative novel α-glucosidase inhibitors through LC-MS-based metabolomics and molecular docking. Tan et al. (2026) demonstrated that fermentation of *Premna microphylla* by *Eurotium cristatum* enhanced its antidiabetic activity in a type 2 diabetes mouse model, suggesting that fermentation may be a useful approach to enhance bioactivity.

Strength of Evidence: Moderate, with evidence from both animal models and a small human study. However, the human study evaluated grass jelly as a food matrix rather than as a therapeutic agent, and the animal studies used crude extracts. Mechanistic understanding is limited.

5.4. Antihypertensive and Hypocholesterolemic Activity

Ethanol extracts of *M. palustris* induced 36.25% inhibition of angiotensin-converting enzyme at 100 ppm concentration (primary study cited in Rahmah et al. 2022). In vivo studies showed that *M. palustris* treatment led to a 50.01% reduction in cholesterol levels and a 36.47% increase in HDL in Wistar mice over 28 days (primary study cited in Rahmah et al. 2022). These findings suggest potential cardiovascular benefits, though the mechanisms remain unclear, and the crude extract used limits interpretation. For *P. trichostoma*, Novelina and Anggraini (2016) demonstrated that chlorophyll extract significantly suppressed total cholesterol by 35.80%, LDL by 83.65%, and triglycerides by 27.51%, while increasing HDL by 43.22% in hypercholesterolemic rats. These findings suggest that *P. trichostoma* chlorophyll extract has potent hypocholesterolemic activity, potentially through mechanisms involving increased bile acid excretion, inhibition of cholesterol absorption, or modulation of cholesterol synthesis. Deng et al. (2025) investigated the anti-hypercholesterolemic effects of small-molecule pectin from *Premna ligustroides* Hemsl leaves, demonstrating that treatment normalized total cholesterol and alanine aminotransferase levels, reduced inflammatory markers, and promoted growth of beneficial bacteria while suppressing harmful bacteria.

Strength of Evidence: Moderate (antihypertensive) to Moderate-High (hypocholesterolemic). The chlorophyll extract studies are promising but limited by the use of crude extracts.

5.5. Anticancer and Cytotoxic Activity

In vivo models showed that *M. palustris* reduced cancer incidence by 57% and enhanced immune responses by increasing interferon-gamma and cytotoxic T-cell counts (primary study cited in Rahmah et al. 2022). Water extracts showed an IC_{50} of 132.6 μg/mL against HeLa cell lines in cytotoxicity assays (primary study cited in Rahmah et al. 2022). These findings are promising, though the 57% reduction is from a single study and requires confirmation. For *C. barbata*,

Lin et al. (1993) isolated five bisbenzylisoquinoline alkaloids as the active principles responsible for the cytotoxic and antimalarial activities. These alkaloids have been shown to inhibit the growth of various cancer cell lines through multiple mechanisms, including DNA intercalation, topoisomerase inhibition, and apoptosis induction. They represent the most well-characterized bioactive compounds among the three species in terms of mechanism of action, and their high natural abundance makes them attractive candidates for development. Valsan et al. (2025) provided a comprehensive appraisal of bisbenzylisoquinoline alkaloids isolated from the genus *Cyclea* for anticancer potential, emphasizing their promise in combating multidrug resistance.

Nurdin et al. (2017) showed that fermentation supernatants of *P. trichostoma* extract reduced Caco-2 cell viability, suggesting potential colorectal cancer prevention properties. The study demonstrated that cincau increased total SCFA concentration by increasing acetate and propionate, and fermentation supernatants reduced Caco-2 cell viability, suggesting that this Indonesian traditional source of dietary fibre may be protective against colorectal cancer. Nurdin et al. (2018) further evaluated the effects of dietary fibre from green cincau on preneoplastic lesions in an azoxymethane rat model of colon cancer, finding that while all dietary treatments stimulated SCFA production, no treatment significantly protected against aberrant crypt formation. This importantly demonstrates that in vitro findings do not always translate to in vivo efficacy and highlights the need for in vivo validation.

Yang et al. (2024) demonstrated that *Premna puberula* root petroleum ether extracts inhibited proliferation, migration and invasion, and induced apoptosis through the mitochondrial pathway in non-small cell lung cancer A549 cells, with an IC_{50} of 38.01 μg/mL and low toxicity to normal cells (IC_{50} = 76.85 μg/mL). Febriyanti et al. (2025) reviewed the anticancer potential of bioactive compounds in *Premna serratifolia*, *P. odorata*, and *P. tomentosa*, identifying flavonoids, terpenoids, and steroids with diverse actions including cell cycle arrest, apoptosis induction, and inhibition of metastasis.

Strength of Evidence: Moderate. The 57% tumor reduction is from a single in vivo study requiring confirmation. The bisbenzylisoquinoline alkaloids from *C. barbata* are the best-characterized compounds with established mechanisms of action.

5.6. Hepatoprotective Activity

M. palustris extracts rescued the production of antioxidative superoxide dismutase and malondialdehyde in ethanol-stressed rats (primary study cited in Rahmah et al. 2022). Treatment with 135 mg/kg of *M. palustris* supplement produced a significantly lower liver damage of 37.05%, with inhibition of alanine aminotransferase and aspartate aminotransferase (primary study cited in Rahmah et al. 2022). While these findings are promising, the original primary studies should be consulted for detailed methodology. For *C. barbata*, Wang et al. (2019) reported that four isolates showed moderate hepatoprotective activity against APAP-induced toxicity in HepG2 cells, expanding the known phytochemical diversity of this species and revealing new bioactive compounds with hepatoprotective potential.

Strength of Evidence: Low to Moderate. The hepatoprotective claims are largely based on studies cited in a review. The *C. barbata* study uses characterized compounds, providing stronger evidence.

5.7. Gut Microbiota Modulation

M. chinensis polysaccharide administration to mice at 300 mg/kg/day demonstrated that the abundance of Firmicutes, Verrucomicrobiota, and Proteobacteria decreased, while Bacteroidetes abundance increased (Seah et al. 2024a; Seah et al. 2024b). At high doses, MCP increased the number of *Bifidobacterium*, *Lactobacillus*, *Coprococcus*, and *Oscillospira*, while decreasing *Akkermansia*, Clostridiaceae, and *Clostridium*. Concentrations of acetic acid, propionic acid, butyric acid, and total SCFAs were increased in a dose-dependent manner with MCP treatment. These findings have significant implications for gut health, as the modulation of gut microbiota composition and the production of short-chain fatty acids are associated with improved intestinal barrier function, reduced inflammation, and enhanced immune function.

Safety Consideration: The decrease in *Akkermansia* abundance is concerning, as *Akkermansia muciniphila* is generally considered a beneficial bacterium associated with improved metabolic health and reduced inflammation. This finding may represent a safety concern or a limitation of the study. We recommend that future studies determine whether this represents a beneficial or adverse effect in the context of overall gut health, investigate whether the effect is dose-dependent or reversible, assess whether this finding might limit the clinical applicability of grass jelly polysaccharides, and use germ-free animals to distinguish primary effects from secondary effects. Zhu et al. (2026) used a Simulator of the Human Intestinal Microbial Ecosystem model to elucidate the segment-specific metabolism of *Premna microphylla* Turcz. in gastric cancer patients, revealing that components were converted into small-molecule phenolic acids by microbiota, providing insights into how the gut microbiota may metabolize grass jelly compounds.

Strength of Evidence: Moderate. The gut microbiota effects are well-documented in animal models, but the safety implications of the *Akkermansia* decrease require further investigation.

5.8. Other Pharmacological Activities

Mustarichie et al. (2020) investigated the anti-alopecia activity of *C. barbata* leaves, finding that ethanol extract and *n*-hexane fraction at concentrations of 15% and above had hair growth-stimulating activity, with the *n*-hexane fraction having the best activity compared to other fractions and positive control (minoxidil 2%). In a study using a 1:1:1 mixture of *Moringa oleifera*, *Cyclea barbata*, and *Centella asiatica*

leaf extracts, Christyaningsih et al. (2024) investigated the effects on fetal development in malnourished pregnant model mice, finding that the extract mixture significantly improved fetal development and blood protein levels. However, the multi-herb formulation limits attribution of these effects specifically to *C. barbata*; this study provides weak evidence. Pribadi et al. (2017) analyzed the pharmacodynamics of ethanol extract of *C. barbata* leaves on SRF and COX-2 in gastric tissue of mice with NSAID gastropathy, suggesting potential gastroprotective effects. **Table 3** summarizes pharmacological activities with evidence quality ratings, highlighting the need for studies with characterized compounds and in vivo confirmation.

Table 3. Summary of pharmacological activities with evidence quality ratings.

Activity	Species	Best Evidence Type	Key Finding	Evidence Quality*	Key Limitation
Antioxidant	*P. palustre*	In vitro	IC50 2.5 ppm (ABTS)	Low	Assay interference; crude extract
Immunomodulatory	*P. palustre*	In vivo	Edema inhibition	Moderate	Crude extract
Antidiabetic	*P. palustre*	In vivo	37% glucose reduction	Moderate	Crude extract
Antihypertensive	*P. palustre*	In vitro	36.25% ACE inhibition	Low	In vitro only
Hypocholesterolemic	*P. trichostoma*	In vivo	83.65% LDL reduction	Moderate	Chlorophyll extract
Anticancer	*C. barbata*	In vitro	Alkaloid activity	Moderate-High	Characterized compounds
Hepatoprotective	*C. barbata*	In vitro	APAP protection	Moderate	Characterized compounds
Gut microbiota	*M. chinensis*	In vivo	SCFA production	Moderate	Safety concerns (*Akkermansia* decrease)

*Evidence Quality: High = confirmed in multiple independent studies with characterized compounds; Moderate = single in vivo study or characterized compounds in vitro; Low = in vitro only, crude extract, or multi-herb formulation.

Source: Deswati et al. (2024), Widyaningsih et al. (2018), Lim et al. (2018), Novelina and Anggraini (2016), Lin et al. (1993), Wang et al. (2019), Seah et al. (2024a).

6. VETERINARY APPLICATIONS

6.1. Reproductive Applications: Sperm Cryopreservation

Wahjuningsih et al. (2021) investigated the effects of black cincau (*Mesona palustris*) leaf extract supplementation in skim milk yolk-based semen extender on Boer goat sperm cryopreservation. The study used a completely randomized design with 110 sperm samples and four treatments: 0%, 1.5%, 2%, and 2.5% (v/v) black cincau leaf extract. The black cincau extract contained total phenols of 39.79 ± 0.87 mg GAE/g, total flavonoids of 169.50 ± 1.77 mg QE/g, vitamin C of 3.86 ppm, and vitamin E of 147.87 ppm. Treatment with 2% black cincau leaf extract supplementation demonstrated the best results for motility, viability, plasma membrane integrity, and lower MDA levels. The 2% extract-maintained sperm motility at 50.40% post-thawing compared to 43.42% in the control group, viability at 59.21% compared to 51.48% in controls, and plasma membrane integrity at 60.45% compared to 53.23% in controls. MDA levels were lowest in the 2% treatment (6.25 ± 0.12 μM) compared to controls (7.47 ± 0.18 μM). Artificial insemination of 30 female goats using the 2% extract resulted in a conception rate of 80%, compared to 63.33% in the control group.

Pearson's correlation analysis revealed that motility had a significantly positive correlation with viability and plasma membrane integrity, while MDA had significantly negative correlations with motility, viability, and plasma membrane integrity. The study concluded that skim milk yolk base diluent supplemented with 2% black cincau leaf extract has the capability to protect motility, viability, and plasma membrane integrity, decrease MDA levels of sperm after freezing, and increase conception rates, with the antioxidant activity of black cincau extract playing a crucial role in suppressing lipid peroxidation and reducing oxidative stress during cryopreservation (Wahjuningsih et al. 2021).

Strength of Evidence: Strong. This represents one of the strongest pieces of evidence for biological activity of grass jelly compounds in a mammalian system. The study is well-designed, with appropriate controls and statistical analysis. However, the study has limitations including limited statistical power (30 female goats, 15 per group), no reported power calculation, an inferential rather than demonstrated mechanism of action, and no fully established dose-response relationship.

Translational Potential: The compounds responsible for antioxidant activity in sperm cryopreservation (rosmarinic acid, caffeic acid) could potentially be isolated and applied in human reproductive medicine. This application provides a valuable foundation for translational research.

6.2. Poultry Production: Ammonia Reduction and Egg Quality

In a study using a combination of encapsulated black cincau leaves (*Mesona palustris*) and probiotics, Natsir et al. (2018) investigated effects on production performances, yolk

cholesterol content, and ammonia levels in laying hens. One hundred ninety-two laying hens at 28 weeks were used in a completely randomized design with four treatments (0%, 0.5%, 1%, and 1.5% combination) and six replications. The results showed no significant effect on feed intake, feed conversion, hen day production, egg mass, income over feed cost, egg weight, or yolk cholesterol content. However, a significant effect was observed on ammonia levels in excreta. The 1.5% treatment resulted in the lowest ammonia levels (0.80 ppm) compared to the control group (1.42 ppm), representing a 43.7% reduction in ammonia emissions.

Table 4. Registered clinical trials involving grass jelly or related products.

Trial Number	Title	Status	Relevance to Grass Jelly
NCT02875275	Liquid or Solid State of Food on Glycaemia, Lipaemia and Insulinaemia	Completed (2016)	Uses grass jelly as food matrix for glucose delivery; not an investigational product
NCT05202366	An Open-label Study Evaluating the Effectiveness of CGB-400 Topical Gel for Fungal Infection	Completed (2024)	"CGB" may refer to cincau; proprietary composition not disclosed
NCT04605289	Levels of Matrix Metalloproteinase-8 After Intrapocket Treatment in Moderate Periodontitis	Unknown	Uses lemongrass essential oil; demonstrates framework for herbal gel trials
NCT03772405	Effect of the Nasal Gel "Nascum®-Plus" on Allergic Symptoms	Completed (2018)	Physical barrier mechanism; model for natural product evaluation
NCT01569191	Non-Pharmaceutical Treatment of Seasonal Allergic Conjunctivitis	Completed (2012)	Framework for non-pharmaceutical interventions

Source: ClinicalTrials.gov (2012, 2016, 2018, 2024).

Attribution Problem: The reduction in ammonia levels was attributed to the ability of probiotics to maintain intestinal health, reduce the pH of excreta, and suppress the growth of gram-negative bacteria. However, the combination of black cincau with probiotics confounds attribution of the ammonia reduction effect. While the 43.7% reduction is substantial, it cannot be attributed specifically to black cincau, as the study did not include a black cincau-only treatment group. We therefore classify this as weak evidence for black cincau activity specifically. The encapsulation technology using Arabic gum, whey, and butylated hydroxytoluene protected the bioactive compounds and probiotics from degradation during processing and storage. Future studies should include a black cincau-only treatment group to enable attribution of effects.

7. CLINICAL TRIALS: THE TRANSLATION GAP AND REGULATORY PATHWAYS

7.1. Clinical Trial Landscape

A systematic search of the ClinicalTrials.gov database was conducted to identify registered clinical trials involving grass jelly species or their derivatives. The search identified five relevant studies, though none directly involve the three principal grass jelly species as investigational products. This systematic search reveals a profound translation gap for grass jelly research, with only one study (NCT02875275) involving grass jelly as a food matrix and no direct clinical investigations of any grass jelly species as therapeutic agents. **Table 4** summarizes these trials.

NCT02875275 is the most directly relevant to grass jelly research, evaluating the metabolic effects of glucose administered with grass jelly in both liquid and solid forms. This study represents the only registered clinical trial involving grass jelly as a food matrix. However, it does not evaluate grass jelly itself as an investigational product but rather as a food matrix for glucose delivery. It does not evaluate the bioactive compounds in grass jelly, does not assess their bioavailability, and does not measure any biomarkers of the pharmacological activities demonstrated in preclinical studies. The study was completed in 2016 with 23 male participants. Despite these limitations, this study provides indirect evidence on the metabolic effects of grass jelly in humans and could serve as a starting point for future research. For example, the study's findings on the impact of grass jelly as a food matrix on glycemic response could inform the design of future trials investigating the antidiabetic potential of grass jelly compounds.

CT05202366 involves CGB-400, described as a "proprietary eutectic mixture of GRAS compounds." While the specific composition is not disclosed, the acronym "CGB" may stand for "Cincau" or related compounds. If CGB-400 contains compounds derived from or inspired by grass jelly species, this study could represent a translational application. However, proprietary nature prevents independent verification and scientific knowledge generation. We recommend that the composition be disclosed to enable scientific validation. The study was completed in 2024 with 15 participants.

7.2. Regulatory Pathways and Commercialization Barriers

The absence of clinical trials despite extensive preclinical evidence reflects systemic issues in natural product research. However, the path from preclinical evidence to clinical translation requires navigating complex regulatory, intellectual property, and funding landscapes that present unique challenges for botanical products. To support an Investigational New Drug application for a grass jelly-derived therapeutic, specific preclinical studies would be required, including GLP-compliant toxicology studies (acute, subchronic, and chronic toxicity studies in at least two species to establish a No Observed Adverse Effect Level), pharmacokinetic studies (characterization of absorption, distribution, metabolism, and excretion), and Chemistry, Manufacturing, and Controls information (detailed information on the botanical raw material, extraction process, purification methods, characterization of the active compounds, and quality control procedures).

Batch-to-batch consistency is a major regulatory hurdle for botanical products. For grass jelly-derived products, we propose a quality control approach including development of marker compounds (rosmarinic acid and caffeic acid for *P. palustre*, tetrandrine for *C. barbata*, and phytol for *P. trichostoma*), acceptance criteria based on historical batch data, analytical methods such as HPLC-PDA, LC-MS, and HPTLC, and metabolomic fingerprinting, which offers a particularly powerful approach to quality control and is increasingly accepted by regulatory agencies.

Table 5. Mapping material science applications to translational challenges.

Material Science Application	Translational Challenge Addressed	Relevance to Grass Jelly	Key References
Hydrogel development	Bioavailability (controlled release)	*P. trichostoma* polysaccharides	Hendrawan et al. 2019; Hendrawan et al. 2023
Wound healing scaffolds	Topical delivery (low regulatory hurdles)	*P. palustre*, *C. barbata* extracts	Luong and Lin 2025; Nguyen et al. 2026; Sari et al. 2021
Transdermal delivery	Bioavailability (skin permeation)	*P. palustre* polysaccharides	Li et al. 2026
Nanoparticle biosynthesis	Bioactive compound delivery	*P. palustre* aqueous extract	Phuong Uyen Nguyen et al. 2025
3D food printing	Functional food development	*P. trichostoma* hydrogel	Taqdissillah et al. 2026
Energy storage applications	Demonstrates versatility; sustainable development	*C. barbata* biomass	Taer et al. 2026; Zheng et al. 2024

The patentability of natural products presents unique challenges. Viable IP strategies include patenting specific extraction methods, formulations, specific applications, and combinations of compounds. Clinical trials for botanical products typically cost $10–50 million. Potential funding sources include public-private partnerships, philanthropic organizations, NIH and other public funding, and Small Business Innovation Research and Small Business Technology Transfer grants. The absence of clinical trials for grass jelly species reflects not only scientific gaps but also the significant regulatory, IP, and funding barriers that must be overcome. Dianita and Jantan (2017) emphasized that isolated bioactive components should be further subjected to more preclinical studies and elaborate toxicity studies before clinical trials can be pursued, and Sasmita and Ling (2017) concluded that given the apparent safety of *M. palustris* having been utilized throughout the years, future studies are highly recommended, especially within the clinical settings.

Estimated Timeline and Costs: Phase 1 (Compound Identification, Years 1–2): $500,000–1,000,000. Phase 2 (Mechanistic Elucidation, Years 2–4): $1,000,000–2,000,000. Phase 3 (Pharmacokinetics, Years 3–4): $1,000,000–2,000,000. Phase 4 (Translational Validation, Years 4–6): $10,000,000–50,000,000. Phase 5 (Integration and Sustainability, Years 1–6): $2,000,000–5,000,000. Total Estimated Cost: $14.5–60 million over 6 years.

8. MATERIAL SCIENCE AND EMERGING APPLICATIONS

8.1. Framing and Integration

The same gel-forming properties that enable grass jelly's traditional food application also make these polysaccharides valuable for advanced material science applications. These applications—ranging from wound healing scaffolds to transdermal delivery systems—demonstrate the broader potential of these plant resources for sustainable development and human health. Importantly, these material science applications directly inform and support translational development: hydrogel technologies could provide delivery systems for grass jelly bioactive compounds, addressing bioavailability challenges; wound healing applications provide a clear translational pathway with lower regulatory hurdles than systemic therapeutics; and transdermal delivery addresses the pharmacokinetic challenges identified in this

review. **Table 5** summarizes how specific material science applications map specific translation challenge.

8.2. Hydrogel Development for Controlled Release

The gel-forming properties of grass jelly polysaccharides have been exploited in various material science applications relevant to functional food and nutraceutical delivery. Hendrawan et al. (2019) developed a biodegradable *P. trichostoma* extract/polyvinyl alcohol composite hydrogel for controlled-release and water absorption applications, achieving water absorption capacity up to 550% and water retention for almost three weeks. FTIR spectra showed evidence of copolymerization through intermolecular hydrogen bonding. Hendrawan et al. (2023) further developed VOGmC-based composite hydrogels incorporating carbon nanotubes, which increased surface roughness and reduced crystallite size. The addition of KCl into VOGmC7 reduced pore size and increased structural density, while carbon nanotubes interacted physically with VOG to increase surface roughness and reduce crystallite size. Taqdissillah et al. (2026) investigated the feasibility of using *P. trichostoma* as a single-ingredient hydrogel ink for extrusion-based 3D food printing for dysphagia patients, demonstrating that 10 w/v% hydrogels met IDDSI Level 5 criteria, representing an innovative application with potential applications in personalized nutrition and texture-modified foods. Wound Healing Applications

The bioactive compounds in grass jelly species have shown promise in wound healing applications. Sari et al. (2021) developed a novel composite membrane from *C. barbata* pectin blended with chitosan, demonstrating improved thermal stability and better wound closure in vivo. The membrane demonstrated swelling degree of 266%, water vapor transmission rate of 9.68 g/m²h, and porosity of 64%. In-vivo results indicated that the chitosan/pectin membrane immobilized with *Musa Paradisiaca* Linn group had better wound closure with better wound reduction percentage than the gauze-treated wound. Luong and Lin (2025) developed a bilayer hydrogel and nanofiber scaffold infused with *Calophyllum inophyllum* oil and *P. palustre* aqueous extract, achieving 82.19% DPPH scavenging and 98.22% wound closure in a rat model. The bilayer scaffold combined the antioxidant and anti-inflammatory properties of *P. palustre* with the wound healing properties of *C. inophyllum* oil, demonstrating a synergistic effect on wound healing.

Nguyen et al. (2026) developed bilayer scaffolds composed of a collagen sponge layer derived from fish skin and a PVA layer incorporated with *P. palustre* aqueous extract and biosynthesized ZnONPs, exhibiting high flexibility with tensile strength of about 4 MPa and elongation at break of around 300%, rapid fluid absorption, slightly acidic pH (6.5–6.8), excellent biocompatibility (cell viability > 115% after 48 h and hemolytic percentage < 1.5%), strong antioxidant activity (69–70% DPPH and 80% ABTS scavenging), and antimicrobial properties against both Gram-positive and Gram-negative bacteria. Ismail et al. (2020) demonstrated that *C. barbata* extract decreased neutrophil migration and improved neutrophil apoptosis during the inflammatory phase of burn wounds. Xu et al. (2026) developed a bioengineered *Premna microphylla*-silver nanoparticle hydrogel for multidrug-resistant wound management in diabetic therapeutics, achieving 95.6% antibacterial efficiency against MRSA and reducing wound area to only 5.4% of its original size by day 11 in a diabetic wound model.

8.3. Transdermal Delivery and Nanoparticle Biosynthesis

Li et al. (2026) developed natural deep eutectic solvents-polysaccharide/polyvinyl alcohol nano-electrospun membranes with 51.63-fold enhanced solubility and 10.11 ± 0.13 mg/cm² cumulative skin permeation. The study explored the use of *P. palustre* polysaccharides in transdermal drug delivery systems, demonstrating enhanced solubility and skin permeation of poorly water-soluble drugs. The L-proline/lactic acid NADES increased PPP solubility 51.63-fold through hydrogen-bond disruption. Electrospinning with PVA created 40–150 nm diameter nanofibers enabling dual transdermal mechanisms: lactic acid's stratum corneum disruption and sustained nanofiber release, achieving 10.11 ± 0.13 mg/cm² cumulative skin permeation in 24 h. The membranes demonstrated 95.36 ± 0.17% *Staphylococcus aureus* and 93.59 ± 0.15% *Escherichia coli* inhibition, suppressed macrophage nitric oxide by 75.8%, and maintained >90% fibroblast viability.

Phuong Uyen Nguyen et al. (2025) reported the biosynthesis of silver nanoparticles and zinc oxide nanoparticles using *P. palustre* aqueous extract as an eco-friendly alternative to traditional chemical methods. XRD analysis revealed average sizes of 7 nm for AgNPs and 24–44 nm for ZnONPs. AgNPs demonstrated notable antioxidant properties, achieving 70% ± 0.68 DPPH scavenging and 75% ± 0.82 ABTS inhibition at 0.1 mg/mL, while ZnONPs showed superior efficacy with 47.43% ± 0.68 DPPH scavenging and 80% ± 0.82 ABTS inhibition. Antibacterial assays revealed that AgNPs were particularly effective against Gram-positive bacteria, while ZnONPs exhibited activity against both Gram-positive and Gram-negative strains. Nguyen et al. (2025) demonstrated green in situ fabrication of silver nanoparticles coated silk using aqueous leaf extract of *Premna serratifolia* for antibacterial textiles, achieving excellent inhibition of over 99.78% against *S. aureus* and over 99.99% against *E. coli*, persisting even after 5 to 10 washing cycles.

8.4. Energy Storage and Food Applications

Beyond biomedical applications, grass jelly biomass has shown promise in energy storage. Taer et al. (2026) synthesized natural nitrogen-doped hierarchical porous carbon and ZnO derived from *C. barbata* leaves for high-energy symmetric supercapacitors, achieving specific capacitance of 210 F g^{-1} at 1 A g^{-1} and energy density of 21.31 Wh kg^{-1}. Zheng et al. (2024) developed *Premna*-derived heteroatom-doped carbon composites decorated with WO_3 nanoparticles for high supercapacitive performance, achieving a specific capacitance of 528.3 F g^{-1} at 0.5 A g^{-1}. These applications, while

demonstrating the versatility of these plant resources, are tangential to the core focus on food and health and are included briefly to indicate the broader potential. Dai et al. (2026) investigated agar-based gels enriched with *P. palustre* extract, focusing on the effects of concentration and pH on structure, mechanics, and phenolic release. Phenolic compounds in PPE acted as organic cross-linkers and structuring agents, promoting the formation of stable and homogeneous gel networks. Gels containing 20–30% PPE formed denser networks with smaller pores, resulting in slower phenolic release, and PPE exhibited strong antioxidant activity and α-glucosidase inhibitory activity, suggesting these gels could serve as functional food matrices for controlled release and enhanced health benefits.

9. LAND SUITABILITY AND AGRONOMIC CONSIDERATIONS

Darmawan et al. (2019) conducted a land suitability evaluation for grass jelly (*Mesona palustris*) and land conservation in Nawangan, Pacitan Regency. The study used purposive sampling methods to determine sample points, soil sample analysis in the laboratory, and overlay of soil type maps and land use map. The results showed that land suitability classes in Nawangan for grass jelly were very suitable (S1) on land units LaS and LaK, suitable (S2) on land units LiL, LiH, LiS, and LaH, and marginally suitable (S3) on land units LaL and LiK.

The limiting factors for grass jelly cultivation in Nawangan included temperature (not repairable), soil texture (not repairable), slope (8–25% or sloping to rather steep, repairable through terracing), water availability (2056.3 mm/year rainfall, repairable through irrigation), oxygen availability (drainage conditions, repairable through tillage), nutrient retention (pH 6.22–7.00, C-organic ≤1.9%, CEC 7.00–24.8 cmol/kg, repairable through fertilization and organic matter addition), and nutrient availability (available K 0.74 cmol/kg, available P ≤12.5 ppm, total N ≤0.42%, repairable through fertilization). The study recommended land improvement measures including terracing to decrease erosion potential, drainage improvement through soil management practices, addition of animal manure or compost to increase organic carbon and CEC, and fertilization suitable to soil minimum factors. While this study focused on a single location in Indonesia, the findings regarding limiting factors and recommended improvements are likely relevant to grass jelly cultivation in other geographic regions with similar soil and climatic conditions.

Climate change may affect grass jelly cultivation through altered rainfall patterns, increased temperatures, and changes in pest and disease pressure. Future research should assess the vulnerability of grass jelly cultivation to climate change and develop adaptation strategies. Given that temperature is identified as a non-repairable limiting factor, the selection of heat-tolerant cultivars (potentially the triploid and tetraploid cytotypes identified by Zhao et al. 2025) will be important for climate resilience.

10. THE SYSTEMIC GAP AND PROPOSED RESEARCH FRAMEWORK

10.1. Seven Systemic Deficiencies

The field of grass jelly research suffers from seven systemic deficiencies that perpetuate its status as a promising but unvalidated botanical resource. First, the extractology problem refers to the fact that most studies use crude extracts without identification of active compounds, resulting in repetitive studies that fail to advance mechanistic understanding. This is not unique to grass jelly research but is a pervasive issue in natural product studies that limit translational progress. Second, the attribution problem arises because studies using multi-herb formulations cannot attribute observed effects specifically to grass jelly species. This is a significant methodological concern that undermines the evidence base. Third, compound identification gaps persist as no study has definitively identified the specific bioactive compounds responsible for the observed pharmacological activities, although recent metabolomic studies have identified candidate compounds. Fourth, mechanistic uncertainty remains because without identification of active compounds, mechanistic understanding remains limited, though recent transcriptomic and WGCNA analyses have identified potential pathways and hub genes. Fifth, pharmacokinetic absence refers to the fact that no studies have investigated bioavailability, metabolism, tissue distribution, or pharmacokinetics of grass jelly compounds, representing a critical gap for translational development. Sixth, integration fragmentation occurs as research is conducted in disciplinary silos without integration. Seventh, translational failure represents the most significant gap and the ultimate barrier to realizing the therapeutic potential of these plants, as no direct clinical trials have been conducted on any grass jelly species as therapeutic agents.

10.2. Compound Prioritization for Development

Given the hundreds of compounds identified in grass jelly species (1,228 in *P. palustre* alone), prioritizing compounds for development is essential. We propose criteria for selecting lead compounds including potency (lowest IC_{50} values in relevant assays), selectivity (activity against the target with minimal off-target effects), chemical tractability (favorable physicochemical properties for drug development), natural abundance (sufficient quantities to enable isolation and characterization), novelty (novel structures or mechanisms of action), and existing evidence (compounds already linked to specific pharmacological activities).

A critical note on the application of physicochemical criteria: We apply Lipinski's Rule of Five as a guideline, but we acknowledge its limitations for botanical products. Lipinski's Rule was designed for synthetic drugs, not botanical products,

and many clinically used natural products fall outside these parameters. Furthermore, botanicals may act through mechanisms that do not require direct absorption, such as gut microbiota modulation. The criteria should therefore be considered as guidelines for prioritizing compounds for development, not rigid requirements.

Based on these criteria, we propose the following shortlist of candidate compounds. From *P. palustre*, rosmarinic acid (molecular weight 360.3 Da, LogP 2.8) is selected based on high abundance (46.96 μg/mL), well-established antioxidant and anti-inflammatory activities, and favorable chemical tractability. Caffeic acid (molecular weight 180.2 Da, LogP 1.2) is selected based on high abundance (29.29 μg/mL), documented antioxidant and antidiabetic effects, and favorable chemical tractability. α-Bisabolol (molecular weight 222.4 Da, LogP 4.2) is selected based on prominence as a major volatile compound with demonstrated anti-inflammatory and wound healing properties. From *C. barbata*, (+)-*S,S*-tetrandrine is selected based on established anticancer activity, known mechanism of action, and high natural abundance (up to 3% of root material). (-)-Curine is selected based on documented neuromuscular blocking activity and potential for respiratory applications. From *P. trichostoma*, phytol (LogP 7.8, exceeding Lipinski's Rule of Five) is selected based on high abundance (19.06% of identified compounds) and demonstrated antimicrobial and anti-inflammatory properties, though its high LogP suggests potential bioavailability challenges that would need to be addressed through formulation strategies. Chlorophyll (molecular weight 893.5 Da for chlorophyll a) is selected based on high content (1184.475 mg/L) with demonstrated hypocholesterolemic activity, though its large molecular weight and complex structure present formulation challenges.

10.3. Proposed Research Framework

We propose a five-phase research framework to transition grass jelly research from descriptive extractology to mechanistic pharmacology. Phase 1: Compound Identification and Characterization (Years 1–2) would involve comprehensive phytochemical profiling using LC-MS/MS with authentic standards, bioactivity-guided fractionation using preparative HPLC, structure-activity relationship studies, and guidance by the compound prioritization criteria outlined in Section 10.2. Phase 2: Mechanistic Elucidation (Years 2–4) would involve investigation of molecular mechanisms using transcriptomics, proteomics, and targeted pathway analysis, including antioxidant mechanisms (HAT vs. SET, metal chelation, Nrf2/ARE pathway), immunomodulatory mechanisms (NF-κB, MAPK, and JAK/STAT signaling pathways), and gut microbiome modulation through 16S rRNA sequencing and germ-free mouse models. Phase 3: Pharmacokinetics and Bioavailability (Years 3–4) would involve characterization of pharmacokinetics and bioavailability of the active compounds, including in vitro digestion and Caco-2 cell permeability studies, in vivo pharmacokinetic studies in rodent models to determine Cmax, Tmax, AUC, t1/2, and bioavailability, and inclusion of both male and female animals to assess sex-specific differences in pharmacokinetics. Phase 4: Translational Validation (Years 4–6) would involve preclinical safety assessment including acute and subchronic toxicity studies, genotoxicity and mutagenicity assessment, determination of NOAEL, pilot clinical trials in humans to assess safety, tolerability, and preliminary efficacy, and clinical trials designed with sufficient power to detect sex-based differences in response. Phase 5: Integration and Sustainability (Years 1–6) would involve integration of research findings into a comprehensive framework for sustainable development, including land suitability assessments and cultivation trials, cost-benefit analysis, farmer adoption studies and community engagement, and development of specific metrics for success (e.g., number of clinical trials initiated, number of patents filed, area of land under cultivation). **Table 6** summarizes research gaps and priority questions that should guide this framework.

Table 6. Summary of research gaps and priority questions.

Gap	Priority Questions
Compound identification	Which compounds are responsible for observed activities? What are the structure-activity relationships?
Mechanistic elucidation	What are the molecular targets and pathways? Are effects primary (direct interaction) or secondary (fermentation)?
Pharmacokinetics	What is the bioavailability of key compounds? Are there sex-specific differences in ADME?
Safety assessment	What is the NOAEL? Are there toxicities associated with chronic use? What are the implications of the *Akkermansia* decrease?
Clinical translation	How can grass jelly compounds be formulated for clinical use? What are the regulatory pathways?
Sustainability	How can grass jelly be cultivated sustainably? How will climate change affect cultivation?

11. CONCLUSIONS

The literature on grass jelly species, *Platostoma palustre*, *Premna trichostoma*, and *Cyclea barbata*, is extensive but superficial. After a century of research, fundamental questions remain unanswered about the identity of the active compounds, their mechanisms of action, and their clinical potential. Recent advances in genomics, metabolomics, and transcriptomics have begun to address identification and mechanistic gaps, but the translation gap remains substantial and largely unaddressed. The phenomenon of convergent cultural selection—where diverse societies independently recognized similar functional properties in phylogenetically distant plants—represents a remarkable case study in ethnobotany that can inform both drug discovery and

sustainable agriculture. Understanding the biochemical and genetic basis of this convergence may reveal conserved pathways for bioactive compound production that can be exploited for therapeutic development, potentially identifying new compounds or combinations with therapeutic value.

The true novelty lies in a paradigm shift—from descriptive "extractology" to mechanistic pharmacology, from academic publications to real-world impact, from disciplinary silos to transdisciplinary integration. The demonstrated veterinary applications, particularly the improved sperm cryopreservation outcomes, provide a foundation for translational research that can extend to human applications, offering a clear pathway from preclinical discovery to clinical application. We call upon funding agencies to prioritize translational research on grass jelly species. Future studies are highly recommended, especially within the clinical settings and isolated bioactive components should also be further subjected to more preclinical studies and elaborate toxicity study before clinical trials can be pursued.

The field awaits a visionary research program that transforms grass jelly from a local plant with "potential" into a model system for phytochemical discovery, mechanistic understanding, and translational application. Such a program would not only unlock the full potential of these valuable plant resources for human health, animal production, and sustainable development but would also serve as a template for the systematic investigation of other traditional medicinal plants that remain trapped in the cycle of descriptive science.

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AUTHOR CONTRIBUTIONS

Andri Frediansyah: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Denny Kurniawan**: Investigation, Writing – original draft, Formal analysis, Data curation. **Winda Adipuri Ramadaningrum**: Investigation, Writing – original draft, Formal analysis, Data curation. **Solihatun Amidan Amatul Aziz**: Investigation, Writing – original draft, Formal analysis, Data curation. **Angga Rendyantoni Puji Utomo**: Investigation, Writing – original draft, Formal analysis, Data curation. **Ajeng Kusumaningryas Pramono**: Writing – review & editing. **Abdul Rahman Siregar**: Writing – review & editing.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the author(s) used Google Gemini Pro and Trinka AI (Enago) solely to improve the readability, grammar, and language clarity of the text. These tools were not used to generate original research ideas, interpret data, or draw scientific conclusions. Following the use of these tools, the author(s) reviewed and edited all suggestions to ensure scientific accuracy and take full responsibility for the content and integrity of the final publication.

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