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Original Article

Unveiling the Medicinal Potential of Dwarf Water Clover (*Marsilea minuta*): A Comprehensive Review of its Morphological, Anatomical, Phytochemical and Pharmacological Aspects

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ABSTRACT

The dwarf water clover (Marsilea minuta), a versatile aquatic fern, has long been recognized in traditional medicine for its wide-ranging therapeutic applications. This review provides a comprehensive exploration of the botanical, phytochemical, and pharmacological attributes of M. minuta, emphasizing its potential as a source of novel medicinal agents. Botanically, M. minuta is characterized by its distinct four-lobed leaf structure and adaptability to various aquatic and terrestrial environments, making it a sustainable resource for therapeutic exploitation. Phytochemical investigations have revealed the presence of diverse bioactive compounds, including flavonoids, phenolic acids, alkaloids, and saponins, which are associated with its antioxidant, anti-inflammatory, anxiolytic, and hypoglycemic activities. Pharmacological studies underscore its role in modulating key biological pathways, such as neurotransmitter regulation for anxiolytic effects and enzymatic inhibition in carbohydrate metabolism for antidiabetic applications. Preclinical evidence supports its efficacy in treating conditions like anxiety, epilepsy, fever, and inflammation. Additionally, its antioxidant properties suggest a protective role against oxidative stress-related disorders. However, the therapeutic potential of M. minuta is tempered by the limited availability of toxicological and clinical studies, highlighting the need for comprehensive safety evaluations and standardized dosing guidelines. This review also identifies critical gaps in current research, including the need for molecular mechanism elucidation, advanced pharmacokinetic profiling, and well-designed clinical trials. By integrating traditional knowledge with modern pharmacological approaches, M. minuta can be harnessed for its full therapeutic potential. The findings presented in this review aim to serve as a foundation for future studies, paving the way for the development of evidence-based applications of M. minuta in contemporary medicine.

Keywords: Marsilea minuta, phytochemicals, pharmacological potential, antioxidant activity, traditional medicine

INTRODUCTION

Marsilea minuta, commonly known as dwarf water clover or water shamrock, represents a fascinating aquatic pteridophyte within the family Marsileaceae, demonstrating remarkable adaptability across diverse aquatic ecosystems **[1, 2]**. This diminutive heterosporous fern exhibits a distinctive creeping rhizome system that facilitates its spread across wetland substrates, while its characteristic quadrifoliate fronds float delicately on water surfaces or stand erect in shallow conditions **[3, 4]**. The species has evolved specialized anatomical features, including aerenchymatous tissues and modified stomatal complexes, enabling efficient gas exchange and survival in both submerged and emergent conditions **[5, 6]**. Its reproductive biology is particularly intriguing, featuring sporocarps that demonstrate exceptional resilience, capable of remaining viable for extended periods under adverse conditions, thus ensuring species perpetuation across seasonal wetlands **[7, 8]**.

Fig. 1. Dwarf Water Clover (Marsilea minuta)

In the rich tapestry of traditional medicine, *M. minuta* has established itself as a cornerstone therapeutic agent, particularly within the indigenous healthcare systems of Southeast Asian countries like Thailand, Vietnam, and Indonesia, as well as South Asian countries like Bangladesh, India, and Sri Lanka **[9, 10, 11]**. Local healers have long recognized its medicinal value, incorporating the plant into various therapeutic preparations for treating ailments ranging from digestive disorders to inflammatory conditions **[12, 13]**. The ethnomedicinal applications of this species reflect sophisticated traditional knowledge systems developed through generations of empirical observation and practical application **[14]**.

The scientific community's interest in *M. minuta* has experienced a significant surge in recent decades, driven by the growing recognition of its potential therapeutic applications and the global shift toward evidence-based validation of traditional medicines **[15, 16]**. Modern research initiatives have begun unraveling the complex phytochemical profile of this species, revealing a diverse array of bioactive compounds including flavonoids, terpenoids, alkaloids, and phenolic compounds **[17, 18, 19]**. These investigations have expanded beyond mere chemical characterization to encompass detailed pharmacological studies, exploring mechanisms of action and potential therapeutic applications **[20]**. The emerging scientific evidence suggests promising activities including antidiabetic, anti-inflammatory, antioxidant, and antimicrobial properties, warranting further investigation for potential drug development **[21, 22, 23]**.

Contemporary research approaches, utilizing advanced analytical techniques and molecular biology tools, have initiated a new era in understanding *M. minuta's* therapeutic potential **[24, 25]**. This scientific renaissance has been characterized by systematic investigations into its bioactive constituents, safety profiles, and mechanism of action at the cellular and molecular levels [**26]**. The convergence of traditional knowledge and modern scientific methodology has created a robust framework for developing novel therapeutic agents from this historically significant plant [**27, 28]**. This paradigm shift from empirical usage to evidence-based application represents a critical evolution in the understanding and utilization of *M. minuta'*s medicinal properties, potentially paving the way for innovative pharmaceutical developments while simultaneously validating centuries of traditional medicinal knowledge **[29, 30]**.

1. Botanical Description

1.1. Morphological Characteristics

1.1.1. Root System

The root system of *Marsilea minuta* exhibits a complex and highly adaptive architectural organization, characterized by an extensive rhizomatous network that serves multiple physiological and structural functions **[31]**. The primary roots emerge systematically from specialized nodal regions along the creeping rhizome, displaying positive geotropism and forming the foundational framework of the plant's anchorage system **[32, 33]**.

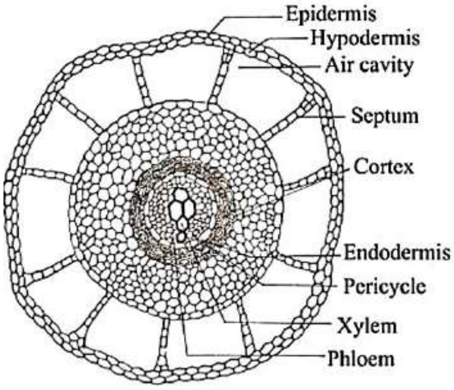

Fig. 2. TS of M. minuta Root

These primary roots, measuring approximately 0.2-0.5 mm in diameter, demonstrate remarkable plasticity in their growth patterns and morphological characteristics depending on environmental conditions **[34]**. They maintain a consistent circadian rhythm in their growth rate, with maximum elongation typically occurring during nocturnal periods. The development of adventitious roots represents a significant adaptive feature of *M. minuta*, occurring at regular intervals of 2-4 cm along the rhizome axis. These adventitious roots demonstrate remarkable physiological adaptability, possessing the capacity to modify their anatomical structure based on environmental conditions **[35, 36]**. In terrestrial environments, they exhibit enhanced vascular tissue development and increased aerenchyma formation, while in aquatic conditions, they show modified cortical tissue arrangements optimized for nutrient absorption from water **[37, 38]**.

The secondary root system comprises an intricate network of fine, dichotomously branching roots that form dense, mat-like structures **[39]**. These secondary roots display sophisticated branching patterns governed by both endogenous hormonal controls and environmental stimuli **[40]**. Their development follows a precise temporal and spatial organization, with lateral root primordia forming in the pericycle region of the primary roots. The branching pattern typically exhibits a hierarchical organization, with secondary roots further subdividing into tertiary branches, creating an efficient soil exploration network **[41, 42]**.

Root hair development in *M. minuta* demonstrates remarkable environmental plasticity, with abundant production in terrestrial forms where they play crucial roles in water and nutrient absorption, soil adherence, and rhizosphere interactions **[43, 44]**. These root hairs typically measure 0.5-1.5 mm in length and exhibit a density of approximately 200-300 hairs per square millimeter of root surface. Conversely, in aquatic forms, root hair development is significantly reduced, reflecting the altered requirements for nutrient and water absorption in aquatic environments **[45]**. This morphological plasticity is regulated by complex interactions between environmental signals and endogenous hormonal pathways, particularly involving auxin and ethylene signaling networks **[46, 47]**.

The entire root system demonstrates remarkable physiological integration, with sophisticated hormone-mediated communication networks coordinating growth and development across different root types **[48]**. This integration enables efficient resource allocation and optimal adaptation to varying environmental conditions, whether terrestrial or aquatic. The root system also exhibits significant symbiotic associations with beneficial soil microorganisms, including arbuscular mycorrhizal fungi, which enhance the plant's nutrient acquisition capabilities and stress tolerance mechanisms **[49, 50]**.

1.1.2. Rhizome Structure

The rhizome system of *Marsilea minuta* displays a complex and well-adapted morphological architecture that significantly contributes to its survival and propagation in diverse aquatic and semi-aquatic environments **[51]**. The creeping rhizome exhibits a pronounced horizontal growth pattern, characterized by internodes measuring 1-3 centimeters in length, which allows for efficient substrate colonization and resource acquisition **[52]**. This growth pattern is particularly advantageous in shallow water bodies and muddy substrates, where the rhizome can effectively anchor the plant while exploring new territories for nutrient acquisition. The dichotomous branching pattern of the rhizome represents a sophisticated evolutionary adaptation, facilitating extensive vegetative propagation and enabling the plant to establish dense populations in favorable habitats **[53, 54]**.

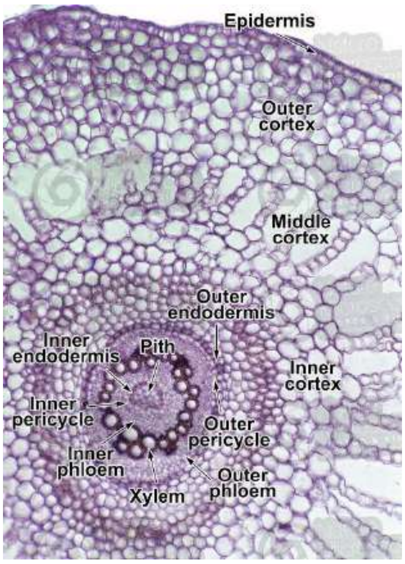

Fig. 3 TS of *M. minuta* Rhizome

This branching mechanism involves the formation of two equal branches from a single growing point, with each branch capable of independent growth and further dichotomous divisions. The rhizome's external appearance undergoes significant ontogenetic changes, transitioning from a light brown coloration in younger segments to a distinctive dark brown or black pigmentation in mature portions, primarily due to the accumulation of phenolic compounds and structural modifications in the epidermal layer **[55,**

56, 57]. The internal anatomy reveals a highly specialized vascular system comprising a modified protostele, which represents an evolutionary advancement in pteridophytes. This vascular arrangement consists of a central xylem core surrounded by phloem tissue, with endodermal and pericycle layers providing additional structural and physiological support **[58]**. The storage tissue system within the rhizome is remarkably developed, containing abundant starch grains arranged in specialized amyloplasts, along with other essential nutrients including proteins and lipids **[60]**. These storage tissues play crucial roles in the plant's survival during unfavourable environmental conditions and support rapid growth during favourable periods. The rhizome also contains specialized secretory cells that produce various bioactive compounds, including flavonoids and terpenoids, which contribute to the plant's chemical defense mechanisms and medicinal properties **[61]**. The epidermal layer of the rhizome is fortified with a thick cuticle and produces root hairs at regular intervals, enhancing water and nutrient absorption while also providing additional anchorage. This sophisticated rhizome structure enables *M. minuta* to adapt to fluctuating water levels and varying substrate conditions, making it a successful colonizer in diverse aquatic ecosystems. Furthermore, the rhizome's architectural features facilitate efficient nutrient translocation and resource sharing between connected ramets, contributing to the plant's clonal growth strategy and ecological success in its natural habitats **[62, 63]**.

1.1.3. Leaf Morphology

The leaves of *Marsilea minuta* exhibit exceptional heterophylly, showcasing remarkable adaptive plasticity in response to varying environmental conditions **[64]**. Each compound leaf manifests as a distinctive quadrifoliate structure, bearing four symmetrically arranged leaflets that are reminiscent of a four-leaf clover. These leaflets demonstrate significant morphological variations depending on their growth environment, with dimensions typically ranging from 0.5 to 1.2 cm in length **[65]**. The leaflets display an obdeltoid to cuneate shape, with the broader end positioned distally and gradually tapering towards the attachment point. The petioles exhibit remarkable environmental adaptability, varying dramatically in length from 3 to 15 centimeters, with the specific length correlating directly with water depth in aquatic environments. This adaptive mechanism ensures optimal leaf positioning for photosynthetic efficiency regardless of water level fluctuations **[66, 67]**.

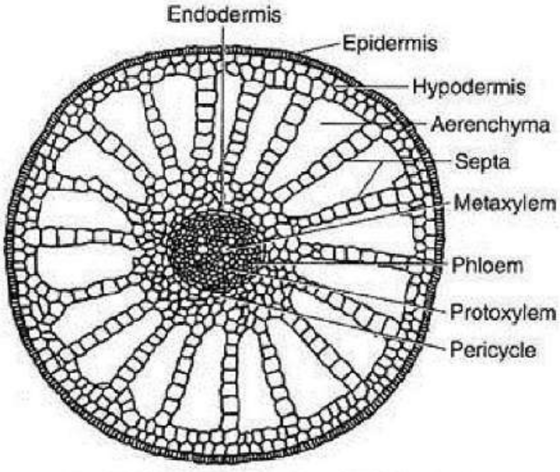

Fig. 4 TS of M. minuta Petiole

The venation pattern within each leaflet is particularly noteworthy, characterized by repeated dichotomous branching that creates an intricate network of vascular tissues. This specialized venation architecture not only provides structural support but also ensures efficient nutrient and water distribution throughout the leaf tissue. A fascinating aspect of *M. minuta*'s leaf anatomy is its stomatal distribution and density, which varies significantly between terrestrial and aquatic forms **[68, 69]**. In terrestrial morphs, stomata are abundantly present on both adaxial and abaxial leaf surfaces, facilitating efficient gas exchange in the atmospheric environment. However, aquatic forms exhibit a marked reduction in stomatal density, particularly on the abaxial surface, representing an evolutionary adaptation to submerged conditions where gas exchange primarily occurs through direct diffusion across the leaf surface [**70, 71]**. The epidermal cells in aquatic forms also tend to be thinner and more elongated compared to their terrestrial counterparts, enhancing the plant's ability to absorb nutrients directly from the aqueous environment. Furthermore, the leaflets demonstrate significant modifications in their internal anatomy, with aquatic forms showing reduced development of palisade mesophyll and increased aerenchyma tissue, while terrestrial forms maintain a more typical dorsiventral leaf structure with well-defined palisade and spongy mesophyll layers **[72]**. This remarkable morphological plasticity in leaf structure represents a sophisticated evolutionary adaptation that enables *M. minuta* to thrive in both terrestrial and aquatic environments, making it an excellent model organism for studying plant adaptation mechanisms **[73, 74]**.

1.2. Reproductive Structures

1.2.1. Sporocarps

The reproductive structures of *Marsilea minuta* exhibit a remarkably sophisticated morphological organization, characterized by distinctive sporocarps that serve as the primary vessels for sexual reproduction **[75]**. These specialized reproductive organs manifest as bean-shaped structures, typically arising from abbreviated peduncles that emerge near the bases of petioles or along the rhizome. The sporocarps demonstrate bilateral symmetry and possess a remarkably resilient outer wall composed of multiple sclerenchymatous layers, presenting a dark brown to almost black coloration at maturity **[76, 77]**.

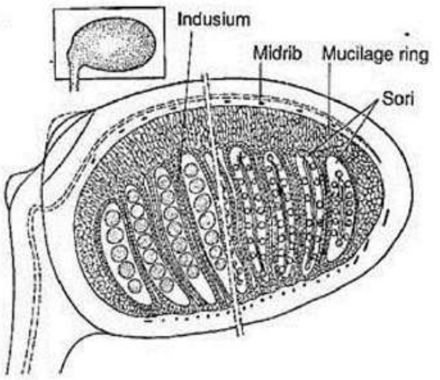

Fig. 5. LS of M. minuta Sporocarp

This protective exterior exhibits intricate ridge patterns that form species-specific geometric configurations, often serving as crucial taxonomic markers for species identification within the Marsileaceae family **[78]**. The sporocarp wall's complex ultrastructure consists of multiple layers: an outer epidermis with thick cuticular deposits, a subepidermal prismatic layer, and several inner layers of sclerenchymatous cells arranged in distinctive patterns that contribute to the sporocarp's mechanical strength and water impermeability **[79]**. Internally, the sporocarp demonstrates a sophisticated compartmentalization system, with multiple sori arranged in two rows along a specialized tissue called the sorophore **[80]**. Each sorus contains both megasporangia and microsporangia, representing an advanced level of heterosporous reproduction among pteridophytes **[81]**. The megasporangia, typically larger and fewer in number, produce single megaspores, while the more numerous microsporangia generate multiple microspores. This dimorphic spore production system represents an evolutionary advancement in reproductive efficiency. The sporocarps typically measure between 2-4 millimeters in length, though size variations can occur based on environmental conditions and geographical location. The external surface ornamentation patterns involve a complex network of raised ridges, tubercles, and sometimes minute depressions that form specific geometric patterns **[82, 83]**. These surface features play crucial roles in water absorption during germination and may influence spore dispersal mechanisms. The sporocarp's internal architecture includes a gelatinous ring structure that swells upon hydration, creating mechanical pressure that facilitates sporocarp dehiscence and subsequent spore release. This sophisticated reproductive system allows *M. minuta* to maintain genetic diversity while ensuring successful propagation in both aquatic and terrestrial environments. The sporocarp's structural adaptations, particularly its hard outer wall and internal compartmentalization, enable long-term spore viability and protection against environmental stressors, contributing to the species' successful colonization of diverse habitats across tropical and subtropical regions **[84, 85]**.

1.2.2. Spores

Marsilea minuta exhibits remarkable heterosporous reproduction, characterized by the production of two distinct types of spores that showcase sophisticated adaptations for survival and reproduction in aquatic environments **[86]**. The microspores, which develop within microsporangia, are spherical structures measuring 25-35 μm in diameter and are produced in substantial quantities, often exceeding 50,000 per sporocarp. These microspores possess a complex wall architecture comprising three distinct layers: the outermost perispore (characterized by its sculptured surface), the middle exospore (composed of sporopollenin), and the innermost endospore (primarily cellulosic in nature). This trilayered structure provides essential protection against environmental stressors while facilitating the eventual release of male gametophytes **[87, 88]**.

In contrast, the megaspores, developed within megasporangia, are significantly larger, oval-shaped structures measuring 400-600 μm in length. Each megaspore demonstrates remarkable organizational complexity, featuring a prominent apical region where archegonia later develop. The megaspore wall exhibits a more elaborate stratification compared to microspores, with specialized layers including an outer epispore (featuring distinctive surface ornamentation), a robust exospore (containing high concentrations of sporopollenin and silica deposits), and an inner endospore layer rich in polysaccharides **[90, 91]**. This intricate wall structure not only provides mechanical protection but also facilitates specific physiological processes essential for germination **[92]**.

The spore germination process in *M. minuta* is particularly fascinating, showing sophisticated adaptation to its aquatic habitat. Upon hydration, both spore types undergo carefully orchestrated developmental sequences **[93]**. The microspores initiate rapid germination within 6-12 hours of hydration, releasing small, reduced male gametophytes that produce motile spermatozoids **[94]**. The megaspores, however, demonstrate a more complex germination pattern, requiring 12-24 hours of hydration before initiating development. During germination, the megaspore undergoes controlled wall rupture at the apical region, followed by the emergence of a female gametophyte bearing archegonia. This temporal separation in germination timing represents an evolutionary adaptation that optimizes reproductive success by ensuring the mature development of female gametophytes before the release of male gametes **[95, 96]**.

The entire reproductive cycle is further enhanced by various structural and physiological adaptations. The spore walls contain specific compounds, including phenolics and sporopollenin, which provide protection against UV radiation and microbial degradation **[97]**. Additionally, the spore surfaces feature specialized structures that facilitate water absorption and regulate gas exchange, crucial for successful germination. The presence of lipid bodies and starch reserves within the spores ensures sufficient energy resources for the developing gametophytes, while specialized proteins and enzymes facilitate the controlled breakdown of wall materials during germination **[98, 99]**.

This sophisticated reproductive system, characterized by distinct spore types with specialized structures and germination mechanisms, exemplifies the evolutionary adaptations that have enabled *M. minuta* to successfully colonize and reproduce in various aquatic environments, contributing to its widespread distribution across tropical and subtropical regions **[100, 101]**.

1.3. Anatomical Features

1.3.1. Stem Anatomy

The anatomical investigation of *Marsilea minuta* reveals a complex and well-organized internal structure characteristic of advanced pteridophytes. The outermost layer comprises a distinctly organized epidermis fortified with a substantial cuticle layer, which serves multiple functions including mechanical protection and regulation of water loss through transpiration **[102]**. This cuticular layer demonstrates significant thickness variation between terrestrial and submerged forms, exhibiting adaptive plasticity to different environmental conditions. The epidermal cells are arranged in a compact, continuous layer with specialized guard cells forming stomata, whose frequency notably varies between the adaxial and abaxial surfaces **[103]**.

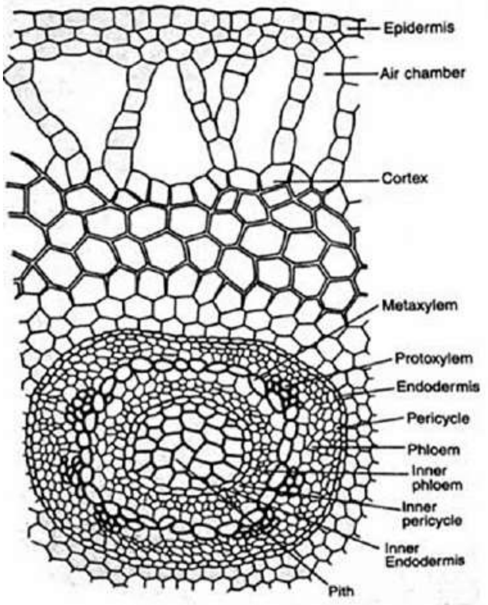

Fig. 5. TS of M. minuta Stem

Beneath the epidermis lies a remarkably differentiated cortex, which is clearly demarcated into outer and inner regions. The outer cortical region consists of 3-5 layers of collenchymatous cells with pronounced corner thickenings, providing mechanical support while maintaining tissue flexibility. In contrast, the inner cortical region exhibits large, thin-walled parenchymatous cells arranged with conspicuous intercellular spaces forming aerenchyma, particularly well-developed in submerged portions of the plant **[104, 105]**. This adaptation facilitates efficient gas exchange and provides buoyancy in aquatic environments. A well-defined endodermis with prominent Casparian strips separates the cortex from the central stele, playing a crucial role in selective nutrient transport and water regulation. The Casparian strips, composed of suberin and lignin deposits in the radial and transverse walls, create an efficient barrier controlling the movement of substances between the cortex and stele **[106]**. The central stele demonstrates a sophisticated organization with xylem elements arranged in a characteristic V-pattern, a feature distinguishing *M. minuta* from other species within the genus. The metaxylem vessels, larger in diameter compared to the protoxylem, are positioned towards the arms of the V, while smaller protoxylem elements are located at the base, indicating an exarch maturation pattern **[107]**. The phloem tissue is strategically distributed in a peripheral pattern around the xylem, consisting of sieve cells and companion cells, optimizing the transport of photosynthates throughout the plant body. This vascular arrangement maximizes the efficiency of water and nutrient transport while maintaining structural integrity. Between the xylem and phloem, a layer of cambiform cells facilitates limited secondary growth, an unusual feature among pteridophytes **[108, 109]**. The entire stele is encased in a distinct pericycle, composed of one to two layers of parenchymatous cells, which maintains the potential for lateral root initiation. This intricate anatomical organization reflects the evolutionary adaptations of *M. minuta* to its amphibious lifestyle, enabling efficient resource allocation and structural support in both aquatic and terrestrial environments.

1.3.2. Leaf Anatomy

The leaf structure of *Marsilea minuta* exhibits remarkable aquatic adaptations that showcase the species' evolutionary success in both aquatic and semi-aquatic environments. The most notable adaptation is the significant reduction in cuticle thickness, particularly in submerged leaves, which facilitates enhanced gas exchange and nutrient absorption directly from the surrounding water **[110, 111].** This reduced cuticle, ranging from 0.5-2.0 µm in thickness, is complemented by a modified epidermal layer featuring specialized cells that optimize the plant's interaction with its aquatic medium. The development of aerenchyma tissue represents another crucial adaptation, forming an intricate network of interconnected air channels throughout the leaf tissue. These aerenchymatous spaces, which can occupy up to 40% of the leaf volume, not only provide buoyancy but also ensure efficient gas exchange and oxygen transport to submerged plant parts, enabling survival in oxygen-depleted aquatic environments. The chlorenchyma arrangement in *M. minuta* leaves demonstrates remarkable plasticity, with palisade cells showing variable arrangements depending on the degree of submergence **[112, 113]**.

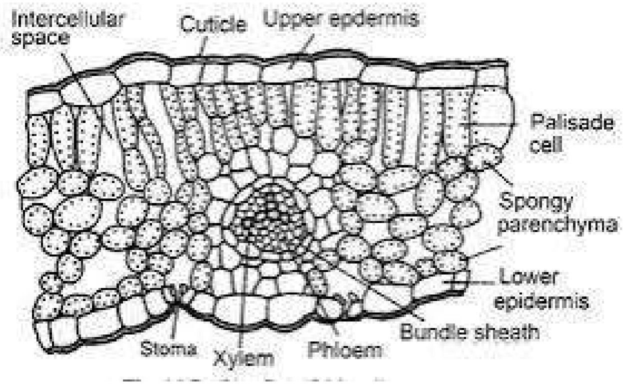

Fig. 6. TS of M. minuta leaf

In fully submerged leaves, the palisade tissue becomes more compact and exhibits a modified orientation to maximize light capture under water, while maintaining sufficient intercellular spaces for gas exchange. The presence of specialized mechanical tissues at leaflet joints represents an intricate adaptation that allows the four leaflets to respond to water movement and light conditions. These joints contain collenchymatous and sclerenchymatous tissues arranged in a distinctive pattern, enabling the leaflets to fold together during unfavorable conditions or at night, and to spread horizontally when environmental conditions are optimal. The vascular bundle patterns in *M. minuta* leaves show unique modifications that differ significantly from terrestrial ferns. The primary vein divides dichotomously within each leaflet, forming a complex network of smaller veins with enhanced xylem elements for water transport and modified phloem tissue for efficient nutrient translocation **[114, 115]**. The bundle sheath cells surrounding these vascular tissues are notably enlarged and contain numerous chloroplasts, contributing to the plant's photosynthetic efficiency in aquatic conditions. Additionally, the presence of hydropoten cells in the epidermal layer facilitates selective ion absorption and secretion, maintaining optimal osmotic balance in varying water conditions **[116]**. These structural modifications collectively demonstrate the sophisticated level of adaptation that

M. minuta has evolved to thrive in its aquatic habitat while maintaining the flexibility to survive in temporarily dry conditions, making it an excellent example of evolutionary adaptation to amphibious environments.

1.4. Growth and Development

1.4.1. Developmental Stages

Marsilea minuta, commonly known as water clover, has a unique and intricate life cycle that reflects its adaptability and biological complexity. The life cycle can be broadly categorized into distinct developmental stages, each characterized by specific biological processes and time frames, influenced by environmental conditions such as temperature, light, and moisture availability **[117, 118]**. The life cycle begins with the **spore germination phase**, a critical initial stage lasting approximately 3 to 5 days under optimal conditions. Spores, which serve as the reproductive units of this fern, are typically dispersed in aquatic or moist environments. Upon encountering favorable conditions, these spores undergo germination **[119]**. The process involves the absorption of water, metabolic activation, and the emergence of the prothallus, a small, flat, green structure that serves as the gametophyte. Successfulgermination is influenced by factors such as pH, temperature, and the availability of nutrients, which collectively dictate the viability and growth rate of the gametophyte **[120]**.

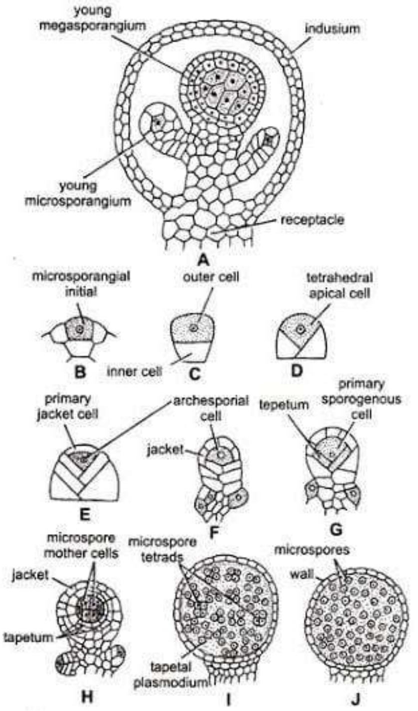

Fig. 7. Developmental stage of M. minuta Microsporangium and Megasporangium

Following spore germination, the **gametophyte development phase** occurs over 10 to 15 days. During this stage, the prothallus matures and develops reproductive structures known as antheridia and archegonia, which produce male and female gametes, respectively. This phase is crucial for sexual reproduction, as the motile sperm cells require a thin film of water to swim toward the archegonia to fertilize the egg cells **[121, 122]**. This dependence on water highlights the evolutionary significance of *Marsilea minuta*'s aquatic or semi-aquatic habitats. Successful fertilization marks the transition to the next stage of development. The fertilized egg, or zygote, then progresses into the **young sporophyte establishment phase**, which spans approximately 20 to 30 days. During this stage, the sporophyte, representing the diploid phase of the life cycle, begins to emerge from the gametophyte **[123, 124]**. This young sporophyte is initially reliant on the gametophyte for nutrients but gradually develops its independent structures, such as roots, stems, and fronds. These structures enable the plant to anchor itself in the substrate and initiate photosynthesis, ensuring its survival and growth. The successful establishment of a young sporophyte depends heavily on environmental conditions, particularly light intensity and water quality **[125]**.

The final phase, the **mature plant development phase**, takes around 45 to 60 days. During this stage, the sporophyte achieves full maturity, characterized by the production of well-developed leaves and reproductive structures known as sporocarps. These sporocarps produce and release spores, thereby completing the life cycle and facilitating the continuation of the species. The mature plant also plays a vital ecological role by contributing to the aquatic ecosystem, serving as a habitat for microorganisms, and influencing nutrient cycling **[126, 127]**.

1.4.2. Environmental Responses

Marsilea minuta, exhibits remarkable adaptability to its environment. This adaptability is driven by its ability to undergo physiological and morphological changes in response to varying environmental conditions **[128]**. These adaptive strategies enable the plant to thrive across diverse habitats, making it a versatile species with considerable ecological significance.

One notable adaptation of *M. minuta* is its ability to rapidly elongate its petiole in response to changes in water levels. This characteristic allows the plant to maintain optimal positioning of its leaves for photosynthesis and gas exchange, irrespective of fluctuating water depths. By extending the petiole, the plant ensures that its photosynthetic apparatus remains above water, maximizing exposure to sunlight **[129, 130]**. This dynamic adjustment in growth is regulated by hormonal changes, particularly the involvement of auxins and gibberellins, which promote cell elongation in response to submergence or water scarcity. Another significant adaptation is the diurnal movement of its leaves. The leaflets of *M. minuta* exhibit nyctinastic movements, unfolding during daylight to capture sunlight for photosynthesis and folding at night to minimize water loss and reduce exposure to nocturnal predators or adverse environmental factors **[131]**. These movements are governed by changes in turgor pressure within specialized cells at the base of the leaflets, known as pulvini. This adaptation highlights the plant's efficient energy conservation mechanisms and its ability to synchronize physiological processes with external environmental cues **[132]**.

The plant also demonstrates a remarkable ability to modify its leaf structure under different light intensities. In high light conditions, *M. minuta* develops thicker, more robust leaves with increased pigmentation to prevent photodamage and optimize photosynthetic efficiency **[133]**. Conversely, under low light conditions, the plant produces thinner leaves with larger surface areas to maximize light capture. These structural modifications underline the plasticity of the plant's photosynthetic machinery and its ability to adapt to varying light environments **[134]**.

Furthermore, *M.* minuta exhibits altered reproductive timing in response to environmental cues, ensuring its survival and reproductive success. The plant can modulate its spore production based on factors such as water availability, temperature fluctuations, and seasonal changes **[135]**. For instance, in favorable conditions, the plant prioritizes vegetative growth and reproduction, while during adverse conditions, it enters a dormant phase, conserving resources and ensuring the survival of reproductive structures like spores. These adjustments underscore the plant's capacity to anticipate and respond to environmental challenges, ensuring long-term population stability **[136, 137]**.

In summary, the adaptive strategies of *M. minuta* reflect a finely tuned interplay between morphological, physiological, and reproductive mechanisms. By elongating its petiole in response to water level changes, displaying diurnal leaf movements, modifying leaf structure under varying light intensities, and altering reproductive timing based on environmental cues, *M. minuta* exemplifies the resilience and versatility of aquatic ferns **[138, 139]**. Understanding these adaptations not only highlights the ecological significance of this plant but also provides insights into its potential applications in ecological restoration and aquaculture systems.

2. Phytochemical Composition

Marsilea minuta, also known for its diverse pharmacological properties, the plant has garnered significant attention in the field of phytochemistry. The phytochemical constituents of *M. minuta* are the primary drivers of its therapeutic potential, making it a subject of interest for researchers in natural product chemistry.

2.1. Primary Phytochemical Groups (Secondary metabolites) in *Marsilea minuta*

2.1.1. Flavonoids

Flavonoids are a significant class of phytochemicals found in *Marsilea minuta*, contributing extensively to its medicinal properties. These naturally occurring compounds are renowned for their potent antioxidant activity, which is essential in neutralizing free radicals and mitigating oxidative stress in biological systems. Oxidative stress is implicated in the pathogenesis of various chronic diseases, including cardiovascular disorders, neurodegenerative diseases, and cancer. By scavenging reactive oxygen species (ROS), flavonoids play a critical role in protecting cells from oxidative damage **[140, 141]**.

Research has identified the presence of flavonoids like quercetin and kaempferol derivatives in *M. minuta*, both of which are well-studied for their diverse biological activities. Quercetin, a flavonol, is known for its strong antioxidant capacity, anti-inflammatory action, and ability to modulate immune responses **[142]**. Similarly, kaempferol, another flavonol present in *M. minuta*, exhibits similar antioxidant potential, along with significant anti-inflammatory and antimicrobial properties. These flavonoid compounds contribute to the plant's pharmacological profile, enhancing its therapeutic value **[143]**.

The anti-inflammatory properties of flavonoids in *M. minuta* are particularly noteworthy. Inflammation is a key factor in many chronic conditions, and flavonoids can modulate inflammatory pathways by inhibiting the production of pro-inflammatory cytokines and enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX) **[144, 145]**. This inhibition reduces the release of inflammatory mediators, thereby alleviating symptoms of inflammation. As a result, *M. minuta* has the potential to be utilized in managing conditions like arthritis, inflammatory bowel disease, and other inflammation-related disorders **[146]**.

Furthermore, the antimicrobial activities of flavonoids present in *M. minuta* are significant, as these compounds can disrupt the growth of various pathogenic microorganisms. By targeting bacterial cell walls, altering membrane permeability, and interfering with microbial enzyme activity, flavonoids in *M. minuta* exhibit broad-spectrum antimicrobial effects **[147]**. This makes the plant a potential candidate for developing natural antimicrobial agents, especially in an era where antibiotic resistance is a growing global concern.

In addition to its antioxidant and antimicrobial actions, *M. minuta* 's flavonoids also possess neuroprotective properties. These compounds protect neural cells from oxidative damage, a leading cause of neurodegenerative diseases such as Alzheimer's and Parkinson's disease **[148, 149]**. By reducing oxidative stress and inflammation in the nervous system, flavonoids contribute to maintaining cognitive function and preventing neurodegeneration. Furthermore, flavonoids have been shown to enhance neuronal survival and promote synaptic plasticity, which are critical for learning and memory processes **[150]**.

2.1.2. Phenolic Compounds

Phenolic compounds represent a major group of phytochemicals present in *Marsilea minuta*, known for their powerful antioxidant properties and their capacity to neutralize reactive oxygen species (ROS) **[151]**. These compounds play a critical role in protecting cells from oxidative damage, which is often linked to the development of chronic diseases such as cancer, diabetes, and cardiovascular disorders. The antioxidant activity of phenolic compounds helps in reducing oxidative stress, thereby preventing the harmful effects of free radicals that can lead to cellular and tissue damage **[152, 153]**.

Among the phenolics identified in *M. minuta*, gallic acid and caffeic acid are of particular interest due to their wide-ranging pharmacological properties. Gallic acid, a trihydroxybenzoic acid, is renowned for its strong antioxidant, anti-inflammatory, and antimicrobial activities **[154, 155]**. It acts by scavenging free radicals and inhibiting lipid peroxidation, processes that are essential in preventing the onset of oxidative stress-related disorders. Additionally, gallic acid has been shown to modulate enzymatic pathways that are involved in inflammation, contributing to its anti-inflammatory effects, which are valuable in the treatment of inflammatory diseases **[156]**.

Caffeic acid, another phenolic acid found in *M. minuta*, is similarly noted for its antioxidant properties, as well as its anti-inflammatory, antidiabetic, and anticancer effects. Caffeic acid works by inhibiting ROS production and enhancing the body's antioxidant defense mechanisms, including the upregulation of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase **[157, 158]**. This phenolic compound also exhibits anti-hyperglycemic effects, which are beneficial in managing diabetes. Studies have shown that caffeic acid can improve insulin sensitivity and glucose metabolism, reducing the risk of complications associated with diabetes, such as cardiovascular diseases.

The antioxidant capacity of phenolic compounds like gallic acid and caffeic acid not only protects against oxidative stress but also supports vascular health by preventing the oxidation of low-density lipoprotein (LDL) cholesterol, a key factor in the development of atherosclerosis **[159]**. By inhibiting the oxidative modification of LDL, these compounds reduce the risk of plaque formation in blood vessels, which can lead to cardiovascular events such as heart attacks and strokes. Furthermore, the anti-inflammatory effects of these phenolics contribute to the stabilization of vascular endothelium, thereby improving overall cardiovascular function **[160]**.

The therapeutic potential of *M. minuta* in managing chronic diseases like diabetes and cardiovascular disorders is largely attributed to its rich content of phenolic compounds. By mitigating oxidative damage, reducing inflammation, and enhancing metabolic function, these compounds provide a multi-faceted approach to disease prevention and management. The presence of gallic acid, caffeic acid, and other phenolic compounds in *M. minuta* highlights the plant's value as a natural source of bioactive molecules with significant health-promoting properties **[161, 162]**. Continued research into the phenolic profile of *M. minuta* may further elucidate its potential in the development of novel therapeutic agents for a range of oxidative stress-related conditions.

2.1.3. Tannins

Tannins, a diverse class of phenolic compounds, are present in significant quantities in *Marsilea minuta*, playing a crucial role in its pharmacological properties. Known for their strong astringent qualities, tannins contribute to the plant's ability to aid in wound healing by contracting tissues and reducing inflammation **[163]**. This property is especially beneficial in closing wounds, preventing excessive bleeding, and promoting the formation of new tissue. Additionally, tannins have been well-documented for their potent antimicrobial activities, making them effective in inhibiting the growth of various bacteria, fungi, and other pathogens that can cause infections. Their antimicrobial action is primarily due to their ability to bind with microbial proteins and enzymes, thereby disrupting cellular processes essential for microbial survival **[164, 165]**.

The high tannin content in *M. minuta* plays a pivotal role in its inclusion in traditional medicinal practices, where it is frequently used for treating infections and skin ailments. In traditional settings, extracts or preparations made from the plant are applied topically to treat wounds, cuts, and ulcers, taking advantage of the tannins' ability to create a protective barrier over the affected area **[166]**. This helps in minimizing contamination and accelerating the healing process. Moreover, tannins are known to have anti-inflammatory properties, which further enhance the plant's therapeutic value in managing skin conditions, inflammation, and microbial infections **[167]**.

Beyond their wound-healing and antimicrobial properties, tannins also exhibit antioxidant activity, which contributes to their overall therapeutic benefits. By neutralizing free radicals and reducing oxidative stress, tannins support the body's defense mechanisms against cellular damage, particularly in cases where infection and tissue damage are involved. This antioxidant capability adds another dimension to the medicinal use of *M. minuta*, as it suggests potential protective effects on a cellular level, contributing not only to faster recovery from wounds but also to the prevention of further tissue damage during infection or injury **[168, 169]**.

In addition to topical applications, the internal use of tannin-rich extracts from *M. minuta* in traditional medicine highlights their broader systemic effects. The astringent properties of tannins are known to aid in managing conditions like diarrhea and gastrointestinal infections by reducing excessive fluid secretion and tightening mucosal tissues **[170]**. This reflects the versatility of tannins in addressing both external and internal health issues.

Overall, the abundance of tannins in *M. minuta* significantly enhances its medicinal value, supporting its use in both modern and traditional medicine. These compounds not only contribute to wound healing and infection control but also exhibit a wide range of bioactivities, including antioxidant, anti-inflammatory, and astringent effects. The continued exploration of tannins from *M. minuta* may provide further insights into their therapeutic potential, expanding their applications in pharmacology and natural medicine **[171]**.

2.1.4. Alkaloids

Alkaloids represent a complex class of naturally occurring organic compounds characterized by the presence of one or more nitrogen atoms within heterocyclic ring structures. In *Marsilea minuta*, while alkaloid concentrations are relatively modest compared to other bioactive constituents, chromatographic analyses have revealed the presence of specific alkaloid derivatives that contribute to the species' pharmacological profile **[172, 173]**. These nitrogenous compounds demonstrate noteworthy biological activities, particularly in modulating nociceptive pathways and inflammatory cascades. Mechanistically, certain alkaloids isolated from *M. minuta* have been shown to inhibit prostaglandin synthesis and influence cytokine production, thereby contributing to the plant's analgesic and anti-inflammatory properties **[174, 175]**. The structural diversity of these alkaloids, including variations in their ring systems and substitution patterns, likely underlies their distinct molecular interactions with biological targets. Recent phytochemical investigations suggest these compounds may act synergistically with other constituent molecules, though further research is needed to fully elucidate their structure-activity relationships and precise mechanisms of action in therapeutic applications.

2.1.5. Saponins

Saponins, glycosidic compounds characterized by their amphipathic molecular structure, represent a complex class of secondary metabolites isolated from *Marselia minuta* with multifaceted biological significance. These compounds demonstrate remarkable biochemical versatility through their intrinsic surfactant-like properties, which facilitate diverse physiological interactions at molecular and cellular levels **[176, 177]**. Biochemical investigations reveal their capacity to modulate lipid metabolism by interfering with cholesterol absorption and transportation mechanisms, thereby potentially contributing to cardiovascular homeostasis. Immunomodulatory characteristics of saponins are evidenced through their ability to stimulate immune cell proliferation and cytokine production, suggesting potential therapeutic implications in immunological regulation **[178]**. The antimicrobial efficacy of these compounds stems from their structural configuration, enabling membrane disruption and inhibition of microbial growth through surfactant-mediated mechanisms. Moreover, their anti-inflammatory properties are attributed to complex molecular interactions involving signaling pathways and inflammatory mediator suppression. The intricate chemical structure of saponins, comprising hydrophilic glycoside moieties and hydrophobic aglycone regions, enables sophisticated biomembrane interactions, underlining their significant pharmaceutical and nutraceutical potential in contemporary biomedical research **[179]**.

2.1.6. Terpenoids

The terpenoids found in *Marsilea minuta* play a significant role in the plant's aromatic characteristics and therapeutic potential. These natural compounds, which encompass monoterpenes and diterpenes, are widely recognized for their diverse biological activities. Notably, they have demonstrated anti-inflammatory, antimicrobial, and antispasmodic effects, which contribute to the plant’s medicinal value **[180, 181]**. The anti-inflammatory properties of terpenoids help reduce inflammation, while their antimicrobial action aids in combating infections caused by various microorganisms. Additionally, the antispasmodic activity of these compounds helps in alleviating muscle spasms and related discomforts. Due to these pharmacological effects, M. minuta has been traditionally utilized in treating ailments associated with the respiratory and gastrointestinal systems, where its terpenoid content plays a crucial therapeutic role. The plant's ability to address conditions such as bronchitis, cough, and digestive issues can be linked to these bioactive terpenoids, making M. *minuta* a valuable resource in herbal medicine **[182, 183]**. Thus, the presence of terpenoids enhances its application in managing a range of health disorders.

2.2. Primary Metabolites

Marsilea minuta, a widely recognized aquatic fern, is an important dietary and medicinal resource due to its rich nutritional composition. Recent investigations have highlighted its significant concentrations of macronutrients and essential biomolecules. Proteins, which play a crucial role in cellular repair and metabolic functions, are present in the plant at levels ranging from 15% to 20% of its dry weight **[184]**. This protein content positions *M. minuta* as a valuable plant-based protein source, especially for regions with limited access to animal-derived proteins.

Carbohydrates, the primary energy-providing biomolecules, are abundantly found in *M. minuta,* constituting approximately 45% to 50% of its dry weight. This high carbohydrate content underscores the plant's potential as an energy-dense food resource, which could be particularly advantageous in addressing caloric deficiencies in undernourished populations **[185]**. Additionally, *M. minuta* contains 12% to 15% dietary fiber by dry weight. The dietary fiber contributes to gastrointestinal health by improving bowel movements, reducing cholesterol levels, and maintaining blood sugar stability, thus rendering *M. minuta* beneficial for individuals with metabolic disorders.

Beyond its macronutrient profile, *M. minuta* also contains notable quantities of essential fatty acids, particularly α-linolenic acid, a precursor of omega-3 fatty acids. Essential fatty acids are crucial for maintaining cell membrane integrity, regulating inflammatory responses, and supporting cardiovascular and neurological health. The presence of α-linolenic acid in *M. minuta* enhances its nutritional value and potential as a functional food.

Overall, the unique nutrient composition of *M. minuta*, including its balanced profile of proteins, carbohydrates, dietary fiber, and essential fatty acids, highlights its multifaceted benefits. Its consumption could address various nutritional deficiencies while promoting overall health and well-being, making it an attractive candidate for both dietary supplementation and therapeutic applications. Further research into its bioactive compounds and mechanisms of action could broaden its utility in food science and medicinal contexts.

Table No. 1. Nutritional and Phytochemical Composition of Marsilea minuta

Metabolite Category	Specific Compounds	Concentration Range	Potential Biological Functions
Primary Metabolites			
Proteins	- Total protein content	15-20% dry weight	Enzymatic catalysis, structural support, cellular signaling
Carbohydrates	- Total carbohydrate content	45-50% dry weight	Energy storage, structural components, cellular recognition
Dietary Fiber	- Soluble and insoluble fiber	12-15% dry weight	Gastrointestinal health, microbiome modulation
Essential Fatty Acids	- α-Linolenic acid (omega-3)	2-5% dry weight	Anti-inflammatory, cardiovascular health support
Secondary Metabolites			
	- Quercetin	0.5-1.2 mg/g	Antioxidant, anti-inflammatory properties
Flavonoids	- Kaempferol	0.3-0.9 mg/g	Cellular protection, potential anticancer activity
	- Flavonoid glycosides	1-2% dry weight	Enhanced bioavailability, metabolic regulation
Phenolic Compounds	- Gallic acid	0.2-0.6 mg/g	Radical scavenging, antimicrobial activity
	- Caffeic acid	0.1-0.4 mg/g	Neuroprotective, metabolic modulation
Terpenoids	- Marsilenone	Trace amounts	Potential cellular signaling modulation
	- Marsileanolide	Trace amounts	Possible hormonal regulatory functions
Steroids	- β-Sitosterol	0.5-1.0 mg/g	Cholesterol metabolism, anti-inflammatory
	- Stigmasterol	0.3-0.7 mg/g	Potential cardiovascular protective effects
Alkaloids	- Undefined nitrogen compounds	Trace amounts	Potential neurological and metabolic interactions

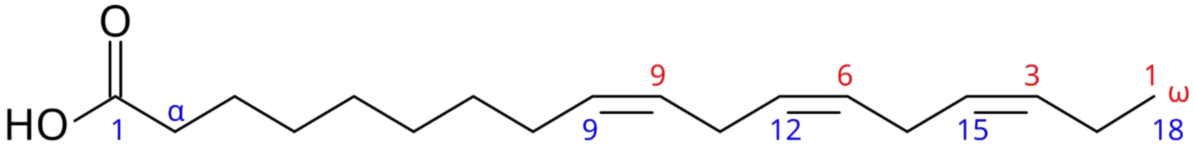

Fig. 9. α-Linolenic acid (omega-3)

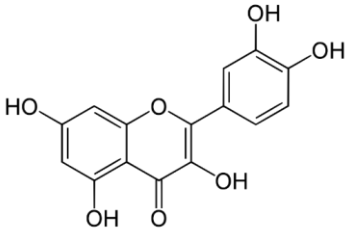

Fig. 10. Quercetin

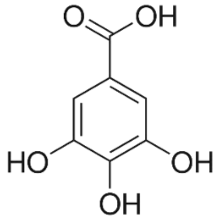

Fig. 11. Gallic Acid

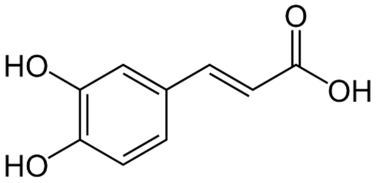

Fig. 12. Caffeic acid

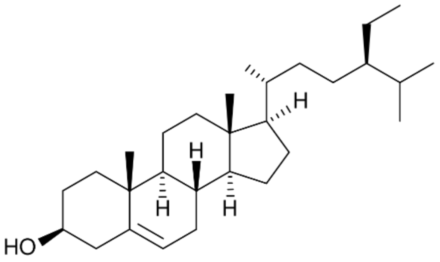

Fig. 12. β-Sitosterol

2.3. Applications of Phytochemical Constituents in *Marsilea minuta*

The diverse and abundant phytochemical constituents of *Marsilea minuta* highlight its multifaceted therapeutic applications. The synergy between its primary and secondary metabolites underpins its pharmacological potential, making it a promising natural resource in healthcare and medicine. The following sections detail the key applications of its phytochemicals, emphasizing their mechanisms of action and potential benefits.

2.3.1. Antioxidant Activity

The significant levels of flavonoids, phenolic compounds, and tannins in *M. minuta* contribute substantially to its antioxidant properties. These compounds neutralize reactive oxygen species (ROS) and prevent oxidative stress, which is a major contributor to aging and chronic diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders **[186, 187]**. Flavonoids like quercetin and kaempferol have demonstrated potent free-radical scavenging activities, protecting cells from oxidative damage. Phenolic acids, including gallic acid and caffeic acid, further enhance the plant's antioxidant efficacy by stabilizing ROS and repairing oxidized biomolecules. The cumulative effects of these bioactives make *M. minuta* a valuable candidate for antioxidant-rich supplements and functional foods **[188]**.

2.3.2. Anti-inflammatory Effects

The anti-inflammatory potential of *M. minuta* is driven by bioactive compounds such as alkaloids, saponins, flavonoids, and terpenoids. These metabolites modulate inflammatory pathways by inhibiting the production of pro-inflammatory mediators like tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1β, IL-6) **[189]**. For instance, terpenoids such as marsilenone and marsileanolide have been identified as key agents in suppressing the activation of nuclear factor kappa B (NF-κB), a central regulator of inflammation **[190]**. The plant's ability to reduce inflammatory responses makes it suitable for managing conditions such as arthritis, asthma, and other chronic inflammatory disorders.

2.3.3. Antimicrobial Properties

The antimicrobial activity of *M. minuta* stems from its secondary metabolites, including tannins, terpenoids, and alkaloids, which interfere with the growth and survival of pathogens **[191]**. Tannins exert their antimicrobial effects by precipitating microbial proteins and disrupting cell membranes, whereas alkaloids inhibit nucleic acid synthesis, leading to impaired pathogen replication. Terpenoids, on the other hand, destabilize lipid bilayers, further compromising microbial integrity. Experimental studies have shown that *M. minuta* exhibits broad-spectrum activity against bacteria and fungi, suggesting its potential as a natural alternative to synthetic antimicrobial agents for treating infections and as a preservative in food and cosmetic formulations **[192]**.

2.3.4. Neuroprotective Effects

The neuroprotective potential of *M. minuta* is attributed to its high content of flavonoids and phenolic acids. These compounds reduce oxidative stress and inflammation in neuronal tissues, two primary contributors to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease **[193]**. Mechanistic studies have shown that flavonoids enhance mitochondrial function, inhibit neuronal apoptosis, and reduce the aggregation of amyloid-beta plaques. Furthermore, their ability to cross the blood-brain barrier allows them to directly exert protective effects on neuronal cells, potentially delaying cognitive decline and improving memory and learning abilities **[194]**.

2.3.5. Antidiabetic Properties

The phenolic compounds in *M. minuta* contribute to its antidiabetic potential by targeting key enzymes involved in glucose metabolism. Inhibition of α-amylase and α-glucosidase enzymes by these bioactives reduces postprandial glucose spikes, a critical factor in diabetes management. Additionally, flavonoids and phenolic acids enhance insulin sensitivity and protect pancreatic β-cells from oxidative damage, preserving their functionality **[195, 196]**. The plant's antioxidant properties also mitigate secondary complications of diabetes, such as diabetic nephropathy and retinopathy, further highlighting its utility in comprehensive diabetes care.

3.3.6. Wound Healing Properties

Marsilea minuta exhibits notable wound-healing capabilities, facilitated by its tannins, saponins, and flavonoids. These compounds accelerate tissue regeneration by promoting fibroblast proliferation, enhancing angiogenesis, and stimulating collagen synthesis **[197]**. The plant's antimicrobial properties protect wounds from infections, thereby reducing healing time and preventing complications. Topical formulations of *M. minuta* extracts have shown promise in enhancing skin repair and minimizing scar formation, making it a potential ingredient in dermatological products.

The phytochemical richness of *Marsilea minuta* offers a broad spectrum of pharmacological applications. Its antioxidant, anti-inflammatory, antimicrobial, neuroprotective, antidiabetic, and wound-healing properties underscore its therapeutic versatility **[198]**. These findings highlight the plant's potential for integration into natural medicine, functional food products, and pharmaceutical formulations, warranting further research and development.

3. Pharmacological Activities

4.1 Hypoglycemic Potential of *Marsilea minuta*:

Marsilea minuta, a small aquatic fern, has garnered substantial attention in pharmacological research due to its broad spectrum of medicinal properties, particularly its potential as a hypoglycemic agent **[199]**. Hypoglycemia refers to the ability to lower elevated blood glucose levels, a crucial therapeutic goal in managing diabetes mellitus. Diabetes, characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both, is a growing global concern **[200]**. The plant's bioactive compounds have been extensively studied, revealing promising antidiabetic properties through multiple mechanisms, including lowering blood glucose levels, enhancing insulin sensitivity, protecting pancreatic β-cells, and modulating glucose metabolism enzymes **[201]**.

3.1.1. Reduction in Blood Glucose Levels in Diabetic Animal Models

Numerous preclinical studies have demonstrated the efficacy of *M. minuta* extracts in significantly reducing blood glucose levels in diabetic animal models. These findings are particularly relevant in conditions such as type 2 diabetes, where sustained hyperglycemia poses severe health risks **[202]**. Experimental studies employing alloxan- or streptozotocin-induced diabetic rodents have consistently shown that *M. minuta* extracts can lower fasting blood glucose levels effectively. These results suggest that the plant's phytoconstituents, such as flavonoids, alkaloids, tannins, and saponins, contribute to its hypoglycemic action. Flavonoids, in particular, are known to enhance glucose uptake in peripheral tissues, mimicking insulin-like activity. Moreover, the plant's bioactive compounds may delay the absorption of glucose in the intestines, thereby preventing postprandial hyperglycemia—a key target in diabetes management.

3.1.2. Enhancement of Insulin Sensitivity

Improved insulin sensitivity is another critical aspect of *M. minuta*'s hypoglycemic action. Insulin resistance, a hallmark of type 2 diabetes, impairs glucose uptake by cells, leading to elevated blood glucose levels. Studies suggest that *M. minuta* extracts can enhance insulin receptor activity and signaling pathways, improving the cellular uptake of glucose **[203]**. Bioactive constituents like phenolic compounds and flavonoids in the plant are believed to activate pathways such as PI3K-Akt, which are integral to insulin-mediated glucose transport. Additionally, these compounds have been shown to reduce systemic inflammation, a significant contributor to insulin resistance. This dual action of alleviating inflammation and improving insulin sensitivity underscores the plant's potential as an adjunct therapy for diabetes.

3.1.3. Protection of Pancreatic β-Cells

Pancreatic β-cells are responsible for the synthesis and secretion of insulin, and their dysfunction or destruction is a central event in the pathogenesis of diabetes. Oxidative stress, induced by chronic hyperglycemia, is a primary factor leading to β-cell damage. *M. minuta* exhibits potent antioxidant activity, which is crucial for protecting β-cells from oxidative stress-induced apoptosis. The plant's high content of antioxidants, such as polyphenols, ascorbic acid, and flavonoids, neutralizes reactive oxygen species (ROS) and reduces lipid peroxidation. Furthermore, experimental studies have shown that *M. minuta* extracts can enhance the regeneration of pancreatic islets in diabetic animal models, indicating a potential role in promoting β-cell recovery and function **[204, 205]**. This property is particularly significant for addressing the progressive nature of diabetes, where β-cell mass declines over time.

3.1.4. Modulation of Glucose Metabolism Enzymes

The modulation of key enzymes involved in glucose metabolism is another mechanism through which *M. minuta* exerts its hypoglycemic effects. Glucose homeostasis is tightly regulated by the balance between glycogenesis (glucose storage) and glycogenolysis (glucose release). Enzymes such as glucokinase (GK), glucose-6-phosphatase (G6Pase), and phosphoenolpyruvate carboxykinase (PEPCK) play critical roles in these pathways. Studies have shown that *M. minuta* extracts can upregulate the activity of GK, thereby promoting glucose utilization and storage in the liver. Simultaneously, the extracts inhibit G6Pase and PEPCK, reducing hepatic glucose production **[206, 207]**. This dual modulation helps maintain stable blood glucose levels, particularly during fasting and postprandial states. Additionally, *M. minuta* has been reported to enhance the activity of glycogen synthase while inhibiting glycogen phosphorylase, favoring glycogen synthesis over breakdown.

3.1.5. Synergistic Mechanisms and Therapeutic Implications

The multifaceted hypoglycemic effects of *M. minuta* are likely due to the synergistic interaction of its diverse bioactive compounds. The plant's ability to address multiple targets in glucose metabolism—ranging from enhancing insulin sensitivity to protecting β-cells and modulating metabolic enzymes—makes it a promising candidate for holistic diabetes management. Furthermore, its antioxidant and anti-inflammatory properties add an extra layer of therapeutic value, as these factors are often implicated in the complications of diabetes, such as cardiovascular diseases and nephropathy **[208, 209]**. Therefore, *M. minuta* has demonstrated significant hypoglycemic potential through its diverse mechanisms of action. By reducing blood glucose levels, enhancing insulin sensitivity, protecting pancreatic β-cells, and modulating glucose metabolism enzymes, this plant offers a comprehensive approach to diabetes management. While the current findings from preclinical studies are promising, further research, including clinical trials, is essential to validate its efficacy and safety in humans **[210]**. Understanding the molecular basis of its actions and identifying specific bioactive compounds responsible for these effects will pave the way for developing novel phytotherapeutics derived from *M. minuta*. As diabetes continues to pose a global health challenge, plants like *M. minuta* represent an invaluable resource for discovering safer and more effective treatments.

3.2. Anti-inflammatory Activity of *Marsilea minuta*

Marsilea minuta (M. minuta), a member of the Marsileaceae family, is a small aquatic fern with various therapeutic applications in traditional medicine. Among its notable pharmacological properties is its potential to mitigate inflammation, a complex biological response initiated by the immune system in reaction to infection, injury, or other harmful stimuli **[211]**. Chronic or excessive inflammation is implicated in the pathogenesis of numerous diseases, including arthritis, cardiovascular conditions, and neurodegenerative disorders. Recent studies have identified multiple mechanisms through which *M. minuta* exhibits anti-inflammatory activity, making it a promising candidate for the development of natural anti-inflammatory agents.

3.2.1. Inhibition of Pro-inflammatory Cytokines

Pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) play pivotal roles in propagating inflammatory responses. These signaling molecules are secreted by immune cells like macrophages, monocytes, and dendritic cells during inflammation, leading to the recruitment of additional immune cells to the site of injury or infection **[212]**. Excessive production of these cytokines is associated with tissue damage and the progression of inflammatory diseases. Studies on *M. minuta* extracts have demonstrated their ability to significantly downregulate the production of these cytokines, thus reducing inflammation. This effect is believed to be mediated by the suppression of nuclear factor-kappa B (NF-κB), a transcription factor critical for cytokine production and immune response regulation **[213]**.

3.2.2. Reduction of Nitric Oxide Production

Nitric oxide (NO) is another key mediator of inflammation. While physiological levels of NO are essential for vascular homeostasis and immune function, excessive NO production, often triggered by inducible nitric oxide synthase (iNOS), contributes to oxidative stress and amplifies inflammatory responses **[214]**. Experimental findings have shown that *M. minuta* inhibits iNOS expression, leading to reduced NO levels in inflamed tissues. This reduction alleviates oxidative stress and protects cellular components from damage caused by reactive nitrogen species. The plant's phytoconstituents, such as flavonoids and phenolic compounds, are thought to be responsible for this effect due to their ability to scavenge free radicals and regulate enzyme activity **[215]**.

3.2.3. Suppression of Cyclooxygenase-2 (COX-2) Expression

Cyclooxygenase-2 (COX-2) is an inducible enzyme involved in the biosynthesis of prostaglandins, lipid compounds that play a central role in inflammation, pain, and fever. Overexpression of COX-2 is linked to chronic inflammatory conditions and tumorigenesis **[216]**. Extracts of *M. minuta* have been reported to suppress COX-2 expression, thereby reducing the production of prostaglandins. This suppression not only attenuates the inflammatory response but also offers a potential analgesic effect, making the plant beneficial for conditions characterized by pain and swelling. The COX-2 inhibitory activity of *M. minuta* is comparable to that of non-steroidal anti-inflammatory drugs (NSAIDs), but with potentially fewer side effects due to its natural origin **[217]**.

3.2.4. Modulation of Inflammatory Mediators

Inflammatory mediators, including leukotrienes, histamine, and interleukins, orchestrate the various stages of the inflammatory process. The ability of *M. minuta* to modulate these mediators highlights its comprehensive approach to inflammation control. Phytochemical analysis reveals that the plant contains bioactive compounds such as alkaloids, saponins, and terpenoids, which may interact with cellular signaling pathways to downregulate the activity of these mediators. For instance, saponins are known to stabilize cell membranes, reducing the release of histamine and other mediators from mast cells **[218]**. Terpenoids, on the other hand, have been implicated in the inhibition of lipoxygenase, an enzyme involved in leukotriene synthesis.

3.2.5. Mechanisms of Action and Therapeutic Implications

The anti-inflammatory activity of *M. minuta* can be attributed to its multifaceted mechanisms of action, which collectively target different stages of the inflammatory response. Its ability to inhibit pro-inflammatory cytokines and enzymes like iNOS and COX-2 underscores its potential as a natural alternative to synthetic anti-inflammatory drugs. Furthermore, the antioxidant properties of the plant's phytoconstituents contribute to its efficacy by neutralizing oxidative stress, a key driver of chronic inflammation. In preclinical studies, the administration of *M. minuta* extracts has shown promising results in animal models of acute and chronic inflammation, such as carrageenan-induced paw edema and formalin-induced arthritis. These findings suggest that the plant could be developed into therapeutic formulations for managing inflammatory diseases **[219]**. However, further research is necessary to identify the specific bioactive compounds responsible for its effects and to elucidate their molecular targets. Additionally, clinical trials are required to confirm the safety and efficacy of *M. minuta* in humans. Therefore, the anti-inflammatory properties of *Marsilea minuta* make it a valuable resource for the development of natural therapeutic agents. By targeting key mediators and pathways involved in inflammation, the plant offers a holistic approach to managing inflammatory conditions. Its traditional use in ethnomedicine, combined with scientific evidence, underscores its potential as a safe and effective alternative to conventional anti-inflammatory drugs. Further exploration of its pharmacological properties and active constituents will pave the way for its integration into modern medicine.

3.3. Antioxidant Properties of *Marsilea minuta*:

Marsilea minuta, has gained significant attention in the field of pharmacological research due to its potent antioxidant properties. These properties play a crucial role in mitigating oxidative stress, which is implicated in the pathophysiology of numerous diseases, including neurodegenerative disorders, cardiovascular conditions, and cancers. The antioxidant potential of *M. minuta* can be attributed to its ability to neutralize free radicals, modulate inflammatory mediators, enhance cellular defense mechanisms, and chelate metal ions. This discussion provides a detailed overview of these mechanisms.

3.3.1. Free Radical Scavenging Activity

Oxidative stress arises when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their deleterious effects. *M. minuta* exhibits substantial free radical scavenging capacity, primarily due to its rich composition of phytochemicals such as flavonoids, phenolics, and terpenoids. These compounds donate electrons or hydrogen atoms to neutralize unstable radicals like superoxide anions, hydroxyl radicals, and peroxyl radicals, thereby preventing cellular damage **[220]**. In experimental studies, extracts of *M. minuta* have demonstrated high scavenging activity in assays using DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)). The reduction in absorbance in these assays reflects the plant's capacity to stabilize free radicals by converting them into less reactive molecules.

3.3.2. Enhancement of Cellular Antioxidant Enzymes

M. minuta also augments the activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These enzymes are critical components of the cellular defense system, as they catalyze the conversion of harmful ROS into benign substances such as water and oxygen.

- ***Superoxide Dismutase (SOD):***

SOD catalyzes the dismutation of superoxide radicals into hydrogen peroxide and oxygen, thereby preventing the formation of more reactive hydroxyl radicals via the Fenton reaction. Studies suggest that bioactive compounds in *M. minuta* upregulate SOD expression, enhancing its protective efficacy.

- ***Catalase (CAT):***

Catalase further decomposes hydrogen peroxide into water and oxygen, reducing the oxidative burden. The plant's extracts have been shown to restore catalase activity in models of oxidative stress, suggesting its protective role at the cellular level.

- ***Glutathione Peroxidase (GPx):***

Glutathione peroxidase reduces lipid hydroperoxides to their corresponding alcohols and free hydrogen peroxide to water, using glutathione as a substrate. The modulatory effects of *M. minuta* on GPx activity enhance its capacity to prevent lipid peroxidation.

3.3.3. Protection Against Oxidative Stress-Induced Damage

Oxidative stress-induced damage can affect lipids, proteins, and DNA, leading to compromised cellular function and apoptosis. *M. minuta* offers significant protective effects by reducing lipid peroxidation and maintaining cellular integrity.

- ***Lipid Peroxidation Inhibition:***

Malondialdehyde (MDA), a biomarker of lipid peroxidation, is reduced significantly in the presence of *M. minuta* extracts, indicating its efficacy in preserving membrane fluidity and preventing oxidative degradation of lipids.

- ***Protein Protection***:

Oxidative stress can induce protein carbonylation, leading to loss of enzymatic activity and structural dysfunction. The antioxidant properties of *M. minuta* help safeguard proteins by neutralizing ROS before they interact with protein structures.

- ***DNA Integrity:***

ROS can cause strand breaks and mutations in DNA, which are precursors to carcinogenesis and other pathological conditions. The phenolic and flavonoid components of *M. minuta* have been shown to reduce oxidative DNA damage, underscoring its potential as a chemoprotective agent.

3.3.4. Metal Ion Chelation

Transition metals like iron and copper can catalyze the production of ROS through the Fenton and Haber-Weiss reactions. Chelation of these metal ions is an effective strategy to mitigate ROS generation. *M. minuta* exhibits metal ion chelation activity, which contributes to its antioxidant effects **[221]**.

The presence of hydroxyl and carboxyl groups in the phytochemicals of *M. minuta* enables it to bind with metal ions, preventing their participation in redox cycling. This chelation not only reduces oxidative stress but also minimizes metal-induced toxicity, which is particularly relevant in conditions like neurodegenerative diseases where metal dysregulation plays a pivotal role.

So, the antioxidant properties of *M. minuta* are mediated through multiple mechanisms, including free radical scavenging, enhancement of endogenous antioxidant defenses, prevention of oxidative damage, metal ion chelation, and modulation of inflammatory pathways **[222, 223]**. These activities underscore its potential as a natural therapeutic agent for managing oxidative stress-related disorders. Further research into its bioactive compounds, mechanisms of action, and clinical applications could pave the way for its inclusion in nutraceuticals and pharmaceutical formulations.

3.4. Antimicrobial Activity of *Marsilea minuta*

Marsilea minuta, commonly used in traditional medicine, have been extensively studied. These investigations reveal its potential against a wide spectrum of pathogens, including bacteria, fungi, and viruses. The phytochemical constituents of *M. minuta* are believed to play a crucial role in its antimicrobial efficacy, attributed primarily to bioactive compounds like flavonoids, alkaloids, tannins, and saponins. Below is an in-depth exploration of its activity against various microbial groups:

3.4.1. Activity Against Gram-Positive and Gram-Negative Bacteria

The antibacterial potential of *M. minuta* has been assessed in multiple studies using standard microbiological techniques such as agar well diffusion, disc diffusion, and broth dilution assays. The plant extract demonstrates significant inhibitory effects on both Gram-positive and Gram-negative bacteria, which are structurally and functionally distinct groups of microorganisms.

- ***Gram-Positive Bacteria***

Pathogens such as *Staphylococcus aureus* and *Bacillus subtilis* are susceptible to *M. minuta* extracts. The mechanism of action is hypothesized to involve disruption of the bacterial cell wall, inhibition of protein synthesis, or interference with metabolic pathways. The high phenolic content, which has antimicrobial properties due to its ability to induce oxidative stress in bacterial cells, is thought to contribute to its activity **[224]**.

- ***Gram-Negative Bacteria***

Notable targets include *Escherichia coli* and *Pseudomonas aeruginosa*. Despite the protective barrier provided by the outer membrane in Gram-negative bacteria, *M. minuta* extracts exhibit notable activity, possibly due to their ability to penetrate or disrupt this membrane. Alkaloids in the extracts may interfere with bacterial DNA replication, while flavonoids could impair enzymatic functions vital for bacterial survival. Comparative studies indicate that the antimicrobial efficacy against Gram-positive bacteria is generally higher, likely due to structural differences in their cell walls, which are more readily disrupted by plant-derived compounds **[225, 226]**.

3.4.2. Activity Against Fungal Pathogens

The antifungal properties of *M. minuta* have been reported against a range of fungal species responsible for human and agricultural diseases. The fungal species studied include both filamentous fungi and yeasts, such as *Aspergillus niger*, *Candida albicans*, and *Fusarium oxysporum.*

- ***Mechanisms of Antifungal Action:***

The antifungal activity is attributed to the disruption of the fungal cell membrane, primarily through the interaction of bioactive compounds like tannins and saponins with membrane lipids **[227]**. Flavonoids and phenolic acids in *M. minuta* can inhibit fungal spore germination and hyphal growth, thereby preventing the establishment and spread of fungal infections.

3.4.3. Exploration of Antiviral Potential of *Marsilea minuta*

Research on the antiviral properties of *Marsilea minuta*, a widely distributed aquatic fern, has revealed a promising yet underexplored avenue in the field of natural product pharmacology. Preliminary investigations into its bioactivity suggest that this plant contains bioactive compounds capable of inhibiting specific viral pathogens **[228]**. The potential applications of such findings are immense, particularly in the current global scenario where emerging viral threats necessitate the development of novel antiviral agents.

- **Antiviral Spectrum and Target Viruses**

The antiviral activity of *M. minuta* appears to be particularly significant against enveloped viruses. These viruses, characterized by a lipid bilayer surrounding their protein capsid, rely on their envelopes for infection and replication within host cells **[229]**. The bioactive compounds of *M. minuta* seem to interfere with these critical structures, possibly disrupting the lipid envelope or viral proteins essential for host cell attachment. Such an effect can inhibit the ability of viruses to recognize and invade host cells, thereby preventing subsequent replication cycles. In addition to enveloped viruses, evidence suggests that *M. minuta* may also exert activity against non-enveloped viruses. These viruses, though lacking a lipid envelope, depend on their replication machinery to propagate within host cells **[230]**. The plant's bioactive constituents might interfere with these processes, thereby suppressing viral replication. This dual-spectrum activity against both enveloped and non-enveloped viruses underscores the potential versatility of *M. minuta* as a source of antiviral agents.

- **Mechanisms of Action**

The antiviral effects of *M. minuta* are hypothesized to arise from a diverse array of phytochemicals, including polyphenols, flavonoids, alkaloids, and saponins. Each of these compounds may contribute uniquely to the inhibition of viral activity.

- **Polyphenols and Flavonoids:**

These compounds are known for their strong antioxidant properties, but their antiviral mechanisms are particularly intriguing. Polyphenols and flavonoids in *M. minuta* may block viral entry into host cells by binding to surface proteins on the virus or receptors on the host cell membrane. This action could effectively prevent the initial attachment of the virus to the host cell, a crucial step in the infection process **[231]**. For example, flavonoids might interfere with glycoproteins on viral envelopes that mediate host cell recognition, thereby halting the infection at its earliest stage.

- **Alkaloids and Saponins:**

Alkaloids and saponins from *M. minuta* might target the replication phase of the viral life cycle. These compounds are believed to inhibit the enzymatic processes necessary for the transcription and replication of the viral genome. Alkaloids may interact with viral polymerases, essential enzymes for the synthesis of viral RNA or DNA, thereby obstructing the production of new viral particles **[232]**. Saponins, on the other hand, could disrupt the structural integrity of viral capsids or membranes, further compromising the virus's ability to replicate and spread. Therefore the antimicrobial activity of *M. minuta* against bacteria, fungi, and viruses underscores its potential as a versatile natural remedy. Its broad-spectrum activity, coupled with a rich profile of bioactive compounds, makes it a valuable candidate for addressing microbial resistance and developing eco-friendly alternatives to synthetic antimicrobial agents. Future research focusing on its molecular mechanisms and applications could unlock its full potential in medicine and agriculture **[233]**

Table No. II. Pharmacological and Therapeutic Potential of Marsilea minuta: Hypoglycemic, Anti-inflammatory, Antioxidant, and Antimicrobial Properties

Pharmacological Activity	Mechanisms of Action	Key Findings
Hypoglycemic Potential	- Reduction in blood glucose levels in diabetic animal models	- Significantly reduces fasting blood glucose in diabetic rodents.
	- Enhancement of insulin sensitivity	- Improves insulin receptor activity and glucose uptake in cells.
	- Protection of pancreatic β-cells	- Antioxidant properties protect β-cells from oxidative stress, enhancing recovery and function.
	- Modulation of glucose metabolism enzymes	- Upregulates glucokinase (GK) activity, inhibits glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK).
Anti-inflammatory Activity	- Inhibition of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α)	- Downregulates cytokine production, suppressing inflammation.

	- Reduction of nitric oxide (NO) production	- Inhibits iNOS, reducing oxidative stress in inflamed tissues.
	- Suppression of cyclooxygenase-2 (COX-2) expression	- Reduces prostaglandin synthesis, comparable to NSAIDs, with potential analgesic effects.
Antioxidant Properties	- Modulation of inflammatory mediators (leukotrienes, histamine)	- Stabilizes cell membranes, reducing mediator release and inflammatory responses.
	- Free radical scavenging activity	- Neutralizes ROS, preventing cellular damage through its rich phytochemical composition (flavonoids, phenolics).
	- Enhancement of cellular antioxidant enzymes (SOD, CAT, GPx)	- Increases activity of endogenous enzymes to detoxify ROS.
	- Protection against oxidative stress-induced damage	- Reduces lipid peroxidation, protein carbonylation, and DNA damage.
	- Metal ion chelation	- Chelates transition metals, preventing ROS generation and metal-induced toxicity.
Antimicrobial Activity	- Activity against Gram-positive and Gram-negative bacteria	- Effective against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*.
	- Activity against fungal pathogens	- Disrupts fungal cell membranes, inhibiting spore germination and hyphal growth.
	- Exploration of antiviral potential	- Bioactive compounds interfere with viral envelopes, blocking host cell attachment and viral replication.

4. Traditional Medicinal Applications

Marsilea minuta, commonly referred to as the water clover, is an aquatic fern widely distributed across tropical and subtropical regions. For centuries, this plant has been valued in traditional medicine systems for its diverse therapeutic applications. Its extensive use in various cultures underscores its medicinal importance, driven by its phytochemical constituents, which exhibit a range of pharmacological activities. The following sections provide a detailed overview of its traditional uses in managing specific health conditions:

4.1. Treatment of Digestive Disorders

One of the primary traditional applications of *M. minuta* is in the management of digestive ailments. Indigenous practitioners have long utilized its extracts for their carminative and laxative properties. The plant is believed to help alleviate symptoms such as indigestion, bloating, and constipation **[234, 235]**. Decoctions prepared from its leaves are traditionally consumed to soothe gastrointestinal discomfort, enhance bowel motility, and improve digestion. The high fiber content of the plant and its bioactive compounds, such as flavonoids and tannins, may contribute to its digestive benefits by promoting gut health and reducing inflammation in the gastrointestinal tract.

4.2. Management of Respiratory Conditions

In traditional medicine, *M. minuta* has also been employed for addressing respiratory issues, including coughs, colds, and mild bronchial conditions. The plant is thought to act as a mild expectorant, helping to clear mucus and ease breathing difficulties. Herbal infusions made from *M. minuta* are often administered to individuals suffering from asthma and bronchitis, aiming to reduce airway inflammation and improve respiratory function **[236]**. The bioactive constituents in the plant, such as phenolic acids and alkaloids, may have roles in modulating inflammatory pathways, thus contributing to its effectiveness in managing respiratory conditions.

4.3. Wound Healing Properties

The application of *M. minuta* in wound care is another prominent traditional practice. The plant is often used externally in the form of poultices or pastes, which are applied to cuts, burns, and ulcers to facilitate healing.

The wound-healing properties of *M. minuta* are believed to stem from its antimicrobial and anti-inflammatory effects, which help prevent infection and promote tissue repair. Its flavonoid and saponin content may play a significant role in enhancing cellular regeneration and reducing oxidative stress at wound sites.

4.4. Anti-inflammatory Applications

The anti-inflammatory potential of *M. minuta* has been recognized in traditional medicinal practices for treating conditions associated with swelling and pain, such as arthritis and skin inflammations. Herbal preparations of the plant, including teas and topical formulations, are used to alleviate joint pain, muscle soreness, and other inflammatory conditions. Scientific investigations suggest that the plant's secondary metabolites, such as quercetin and kaempferol, might inhibit pro-inflammatory mediators like cytokines and prostaglandins, thereby supporting its traditional use in inflammatory disorders **[237]**.

4.5. Blood Sugar Regulation

In traditional systems of medicine, *M. minuta* is also valued for its potential antidiabetic properties. It has been used to regulate blood sugar levels and manage symptoms of diabetes mellitus. Traditional healers often prescribe decoctions made from the plant's leaves for individuals with high blood glucose levels **[238]**. The plant's efficacy in managing blood sugar may be attributed to its ability to enhance insulin sensitivity and inhibit enzymes involved in carbohydrate digestion, as well as its antioxidant properties, which protect pancreatic β-cells from oxidative damage. Preliminary scientific studies have corroborated its traditional use, highlighting its potential as a complementary therapy for diabetes management [**238]**.

So, the traditional uses of *Marsilea minuta* span a wide range of therapeutic applications, including the treatment of digestive disorders, respiratory ailments, wound healing, anti-inflammatory conditions, and blood sugar regulation. These practices underscore the plant’s importance in traditional medicine and provide a foundation for further pharmacological exploration. Modern scientific studies are beginning to validate its traditional uses, attributing its therapeutic properties to bioactive compounds such as flavonoids, phenolic acids, and alkaloids**[239]**. However, more comprehensive research is needed to fully understand the mechanisms underlying its medicinal effects and to develop standardized formulations for clinical applications. As interest in natural remedies grows, *M. minuta* holds promise as a valuable resource in integrative medicine and drug discovery.

5. Safety Profile and Toxicological Studies of *Marsilea minuta*

Marsilea minuta, has been extensively used for its therapeutic properties, such as anxiolytic, antipyretic, and antidiabetic activities. However, the systematic evaluation of its safety profile and toxicological attributes is still in its early stages. The available data suggests that *M. minuta* demonstrates a favorable safety profile when used in traditional practices. Yet, a comprehensive understanding of its toxicological aspects is imperative for its validation as a safe and effective therapeutic agent.

5.1. Traditional Safety Perception

Historically, *M. minuta* has been regarded as safe for consumption in traditional medicine. Indigenous communities have employed various preparations of this plant, including decoctions and infusions, without reporting significant adverse effects. This long-standing use provides a preliminary indication of its non-toxic nature when consumed in conventional doses. However, it is important to note that anecdotal evidence from traditional practices may not encompass all potential adverse reactions, especially at higher doses or prolonged usage. Therefore, scientific validation of these claims through structured studies is critical.

5.2. Acute and Subacute Toxicity Studies

Limited preclinical studies have been conducted to assess the acute toxicity of *M. minuta*. Animal models, primarily rodents, have been utilized to evaluate the plant’s safety profile. These studies indicate that *M. minuta* exhibits no significant acute toxic effects at moderate doses **[240]**. For example, oral administration of its extracts in animals showed no notable changes in behavior, biochemical parameters, or organ histopathology. The absence of immediate toxicological signs suggests a broad margin of safety for its short-term use.

However, data on subacute and chronic toxicity are scarce. Comprehensive investigations involving repeated dosing over extended periods are essential to determine its long-term safety. Such studies would provide insights into cumulative toxicity, potential bioaccumulation, and effects on vital organs such as the liver, kidneys, and heart **[241]**.

5.3. Need for Comprehensive Safety Evaluations

The current lack of extensive toxicological studies highlights the need for a rigorous evaluation of *M. minuta's* safety profile. Standardized protocols, including the Organization for Economic Co-operation and Development (OECD) guidelines for toxicity testing, should be employed to ensure reliable and reproducible results. These evaluations should focus on various endpoints, including genotoxicity, mutagenicity, and teratogenicity, to identify any latent toxicological risks associated with the plant **[242]**.

Furthermore, the development of standardized dosage guidelines is imperative. The variability in preparation methods and dosing in traditional practices poses a challenge in determining the safe and effective therapeutic range. Pharmacological standardization would involve establishing the optimal dose that maximizes efficacy while minimizing potential risks. This would enable the safe incorporation of *M. minuta* into modern therapeutic protocols.

5.4. Role in Blood Sugar Regulation

One of the promising therapeutic potentials of *M. minuta* lies in its ability to regulate blood sugar levels. Preliminary studies suggest that the plant exhibits antidiabetic properties, likely mediated by its bioactive constituents, such as flavonoids, alkaloids, and phenolic compounds **[243]**. These compounds may enhance insulin sensitivity, inhibit carbohydrate-digesting enzymes, and modulate glucose uptake pathways. However, the exact mechanisms underlying its hypoglycemic effects remain poorly understood.

While the efficacy of *M. minuta* in managing blood sugar levels appears promising, its safety in diabetic populations warrants careful examination. Chronic conditions such as diabetes often involve the use of multiple medications, increasing the risk of herb-drug interactions **[244]**. Hence, evaluating the compatibility of *M. minuta* with standard antidiabetic drugs is crucial to prevent adverse effects or diminished therapeutic outcomes.

5.5. Future Directions

To establish *M. minuta* as a safe and effective therapeutic agent, a multifaceted approach is required. Firstly, extensive toxicological studies should be conducted, encompassing acute, subacute, and chronic toxicity, along with reproductive and developmental toxicity evaluations. These studies should incorporate modern analytical techniques to detect potential toxic metabolites and their impact on cellular and molecular pathways.

Secondly, the pharmacokinetics and pharmacodynamics of *M. minuta* need to be thoroughly investigated. Understanding the absorption, distribution, metabolism, and excretion of its bioactive compounds will provide valuable insights into its safety and efficacy. Additionally, the influence of factors such as age, gender, and pre-existing conditions on its pharmacological actions should be assessed.

Lastly, clinical trials in human subjects are essential to validate the preclinical findings. These trials should aim to establish safe dosage ranges, evaluate potential side effects, and assess the overall therapeutic index of *M. minuta*. Collaboration between traditional medicine practitioners, pharmacologists, and toxicologists would facilitate the translation of *M. minuta*'s traditional knowledge into evidence-based applications. In summary, *M. minuta* demonstrates a favorable safety profile based on its traditional usage and preliminary toxicological studies. However, the existing data are insufficient to fully establish its safety, particularly in long-term or high-dose scenarios. Comprehensive toxicological evaluations, standardized dosage guidelines, and rigorous clinical trials are necessary to bridge this gap. Furthermore, its potential role in blood sugar regulation offers an exciting avenue for therapeutic exploration, provided that its safety and efficacy are confirmed through meticulous research. By addressing these aspects, M. minuta can emerge as a scientifically validated natural remedy with significant pharmacological potential.

CONCLUSION

Marsilea minuta, commonly known as the water clover, is an aquatic fern recognized for its diverse therapeutic applications in traditional medicine. This plant has been widely utilized across various traditional systems for managing conditions such as anxiety, epilepsy, diabetes, fever, and inflammation. The broad spectrum of its traditional uses highlights its pharmacological versatility and potential as a source of novel therapeutic agents. Despite this, the integration of *M. minuta* into modern pharmacological practices remains limited, primarily due to gaps in comprehensive scientific validation of its therapeutic properties and safety profile.

Preliminary studies have shed light on the bioactive constituents of *M. minuta*, including flavonoids, phenolic compounds, alkaloids, and saponins, which are believed to contribute to its pharmacological effects. These compounds have demonstrated promising antioxidant, anti-inflammatory, anxiolytic, and hypoglycemic activities in various in vitro and in vivo models. For instance, the anxiolytic effects of *M. minuta* have been attributed to its modulation of neurotransmitter systems, while its hypoglycemic properties may be linked to the inhibition of carbohydrate-digesting enzymes and enhancement of insulin sensitivity. These findings suggest a solid pharmacological foundation, yet they also underscore the need for further exploration of the molecular mechanisms underlying these effects.

One of the major challenges in utilizing *M. minuta* in modern medicine is the lack of standardized preparation and dosing guidelines. Traditional practices often involve crude extracts or unrefined plant material, which may lead to variability in therapeutic outcomes. Modern pharmacological approaches require the isolation and characterization of active compounds, followed by the development of standardized formulations. These formulations must then undergo rigorous pharmacokinetic and pharmacodynamic studies to determine their absorption, metabolism, distribution, and excretion. Additionally, identifying potential herb-drug interactions is crucial, particularly for patients who may use *M. minuta* alongside conventional medications. Another critical aspect that requires attention is the plant's safety profile. While traditional usage provides an initial assurance of safety, scientific validation through toxicological studies is indispensable. Preliminary toxicological evaluations suggest that *M. minuta* is generally safe at moderate doses, with no significant acute toxicity reported in animal models. However, data on chronic toxicity, reproductive toxicity, and potential genotoxicity remain limited. Comprehensive toxicological studies employing internationally accepted guidelines are essential to establish the plant's safety for long-term use. These studies will also help define its therapeutic window and identify any contraindications.

The therapeutic potential of *M. minuta* can be fully realized only through a multidisciplinary research approach. Integrating ethnopharmacological knowledge with modern analytical techniques will enable a holistic understanding of its properties. Moreover, clinical trials are a critical next step to confirm its efficacy and safety in human populations. Such trials should address key parameters such as dosage optimization, side effect profiling, and therapeutic efficacy for specific conditions. The ultimate goal is to develop evidence-based guidelines that allow for the safe and effective use of *M. minuta* in clinical settings. In conclusion, *M. minuta* stands out as a promising medicinal plant with diverse therapeutic applications. While its traditional usage and preliminary scientific studies highlight significant potential, there is a pressing need for more comprehensive research. This includes in-depth pharmacological, toxicological, and clinical studies to ensure its safe and effective incorporation into modern medicine. With continued scientific exploration, *M. minuta* has the potential to become a valuable resource in the development of new drugs and therapeutic strategies

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