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# Phytochemical Properties and Therapeutic Potential of *Hydrocotyle vulgaris*: A Systematic Review

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**Abstract** *Hydrocotyle vulgaris* has been widely used in various folk remedies, and its rich phytochemical constituents, such as flavonoids, alkaloids, and tannins, have attracted the attention of modern scientific research. This study provides a comprehensive analysis of the phytochemical composition of *Hydrocotyle vulgaris* and its antioxidant, anti-inflammatory, antimicrobial, antiviral, neuroprotective, and cardiovascular health benefits through a systematic review of the existing literature. Various analytical methods, such as UV-visible spectroscopy and high-performance liquid chromatography (HPLC), were evaluated, along with the quantitative analysis of its vitamin content. Additionally, this study delves into how *Hydrocotyle vulgaris* influences cellular metabolism by modulating signaling pathways and gene expression, as well as its role in regulating oxidative stress, immune system function, and inflammatory pathways. Although current research has highlighted its therapeutic potential, more data on its long-term safety and toxicity are required. This study provides a theoretical foundation for the further development and application of *Hydrocotyle vulgaris*, while also exploring its potential in modern drug development through the integration of herbal medicine.

**Keywords** *Hydrocotyle vulgaris*; Phytochemical composition; Antioxidant properties; Signal pathway modulation; Safety

## 1 Introduction

*Hydrocotyle vulgaris* is a perennial herbaceous plant belonging to the family Araliaceae. This plant has been traditionally utilized in various medicinal systems across different cultures. For instance, in Ayurveda, it is known as 'Mandukaparni' and is used to treat ailments such as indigestion, dysentery, and nervous disorders. The plant is also recognized for its neuroprotective properties and has been used as a brain tonic in traditional medicine. Additionally, *Hydrocotyle vulgaris* has been employed by various ethnic communities to treat conditions like gastritis, throat infections, and jaundice (Mandal et al., 2020; Rosli et al., 2022).

The study of the phytochemical properties and therapeutic potential of *Hydrocotyle vulgaris* is crucial for several reasons. Firstly, the plant contains a variety of bioactive compounds, including triterpenoids, flavonoids, and essential oils, which have demonstrated significant pharmacological activities such as antioxidant, antibacterial, and hepatoprotective effects (Ekiert et al., 2020; Ganie et al., 2022). Understanding these properties can lead to the development of new therapeutic agents and enhance the efficacy of existing treatments. Moreover, the plant's traditional uses in treating a wide range of ailments highlight its potential as a source of natural remedies (Hazarika et al., 2020; Kour et al., 2021). Given the increasing interest in natural and alternative medicine, a comprehensive study of *Hydrocotyle vulgaris* can provide valuable insights into its medicinal benefits and applications.

This study systematically analyzes the existing literature on the phytochemical properties and therapeutic potential of *Hydrocotyle vulgaris*, identifying its active compounds and evaluating their pharmacological activities. It documents and analyzes the traditional uses of *Hydrocotyle vulgaris*, integrating these uses with scientific findings to verify its medicinal value. This research provides a comprehensive understanding of *Hydrocotyle vulgaris*, serving as a foundation for future studies and potential clinical applications, while also highlighting gaps in current knowledge and suggesting areas for further exploration to fully uncover the therapeutic potential of this versatile plant.

## 2 Phytochemical Properties of *Hydrocotyle vulgaris*

### 2.1 Identification of key phytochemicals

*Hydrocotyle vulgaris* has been found to contain a variety of phytochemicals that contribute to its therapeutic potential. Notably, the plant exhibits an abundant presence of flavonoids and alkaloids, which are known for their antioxidant and anti-inflammatory properties. There is a trace presence of tannins, which have astringent properties and can contribute to the plant's overall medicinal value (He et al., 2023).

### 2.2 Methods used for phytochemical analysis

The identification and analysis of phytochemicals in *Hydrocotyle vulgaris* have been conducted using several advanced techniques. UV-vis spectroscopy has been employed to evaluate the scavenging activity and antioxidant properties of the plant. This method is effective in determining the absorbance of free radicals, thereby providing insights into the plant's antioxidant capacity (Li et al., 2019). High-Performance Liquid Chromatography (HPLC) has been utilized for the precise identification and quantification of essential vitamins and other phytochemicals. HPLC is particularly useful for separating and identifying compounds in complex mixtures, making it an ideal choice for phytochemical analysis.

### 2.3 Quantitative analysis of essential vitamins

Quantitative analysis of *Hydrocotyle vulgaris* has revealed the presence of several essential vitamins that contribute to its nutritional and therapeutic properties. The plant contains β-carotene at a concentration of 10.4 mg/kg, which is a precursor to Vitamin A and is essential for vision and immune function. Riboflavin (Vitamin B2) is present at 4.08 mg/kg, playing a crucial role in energy metabolism. Vitamin C, known for its antioxidant properties, is found at 70.2 mg/kg, while Vitamin E, another potent antioxidant, is present at 26.9 mg/kg (Cai et al., 2022). These vitamins enhance the plant's potential as a therapeutic agent, particularly in combating oxidative stress and promoting overall health.

*Hydrocotyle vulgaris* is rich in key phytochemicals such as flavonoids, alkaloids, and tannins, which have been identified using UV-vis spectroscopy and HPLC. The plant also contains significant amounts of essential vitamins, including β-carotene, riboflavin, and vitamins C and E, further underscoring its therapeutic potential (Ureta et al., 2018).

## 3 Therapeutic Potential of *Hydrocotyle vulgaris*

### 3.1 Antioxidant and anti-inflammatory properties

Ureta et al. (2018) found that *Hydrocotyle vulgaris* is rich in flavonoids and alkaloids, exhibiting strong free radical scavenging ability and significant antioxidant activity, with an IC50 value of 29.75 and a total phenolic content of 158.13% (Figure 1). In addition, the plant contains β-carotene, riboflavin, vitamins C and E, demonstrating its potential as an antioxidant.

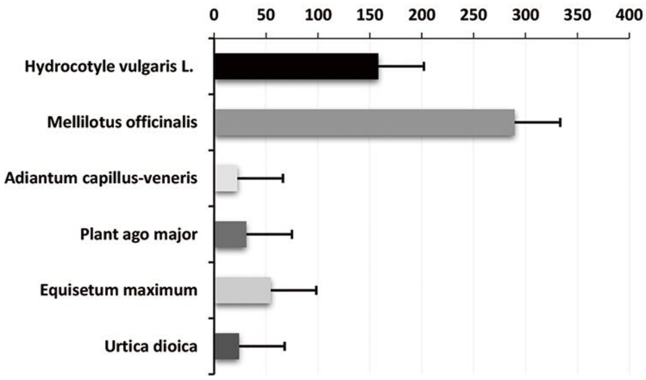


Figure 1 Tested Antioxidant Activity (Total Phenolics) of the *Hydrocotyle vulgaris* L. (Pennywort) extracts as compared with the Phenolics in extracts of different plants (Adopted from Ureta et al., 2018)

The anti-inflammatory action of *Hydrocotyle vulgaris* is primarily mediated through the inhibition of pro-inflammatory cytokines and the modulation of immune cell activity. Studies have shown that plant extracts can reduce the production of cytokines such as TNF-α, IL-6, and IL-8, which are critical mediators of inflammation (Santis et al., 2019; Soleymani et al., 2019; Pandur et al., 2022). Additionally, the activation of antioxidant enzymes like catalase (CAT) and superoxide dismutase (SOD) further contributes to its anti-inflammatory effects by reducing oxidative stress in immune cells (Pandur et al., 2022).

### 3.2 Antimicrobial and antiviral activities

*Hydrocotyle vulgaris* exhibits a broad spectrum of antimicrobial activities against various bacterial and fungal pathogens. The plant's essential oils and extracts have been shown to possess significant antibacterial properties, particularly against resistant strains such as *Pseudomonas aeruginosa* (Patil et al., 2021; Pandur et al., 2022). The antimicrobial efficacy is attributed to the presence of bioactive compounds like thymol and other phenolic compounds, which disrupt microbial cell membranes and inhibit their growth (Pandur et al., 2022).

The antiviral properties of *Hydrocotyle vulgaris* are also noteworthy. Compounds such as hydroxytyrosol have demonstrated antiviral activity against viruses like HIV-1 and Herpes simplex virus by interfering with viral replication and enhancing the host's immune response (Bertelli et al., 2019; Patil et al., 2021). These findings suggest that *Hydrocotyle vulgaris* could be a valuable resource for developing antiviral therapies.

### 3.3 Neuroprotective and cardiovascular benefits

The neuroprotective effects of *Hydrocotyle vulgaris* are primarily due to its antioxidant and anti-inflammatory properties. By reducing oxidative stress and inflammation, the plant's compounds help protect neuronal cells from damage. For example, hydroxytyrosol has been shown to improve endothelial function and decrease oxidative stress, which are critical factors in neuroprotection (Bertelli et al., 2019). Additionally, the modulation of pro-inflammatory cytokines and enhancement of antioxidant enzyme activities contribute to its neuroprotective mechanisms (Santis et al., 2019; Pandur et al., 2022).

*Hydrocotyle vulgaris* also offers significant cardioprotective benefits. The plant's bioactive compounds help improve cardiovascular health by reducing oxidative stress and inflammation, which are key contributors to cardiovascular diseases. Studies have shown that hydroxytyrosol and other phenolic compounds can improve endothelial dysfunction and provide protection against heart diseases (Bertelli et al., 2019). The anti-inflammatory properties further support cardiovascular health by reducing the risk of atherosclerosis and other inflammatory conditions (Patil et al., 2021; Pandur et al., 2022).

## 4 Mechanisms of Action

### 4.1 Cellular and molecular mechanisms

*Hydrocotyle vulgaris*, like many other medicinal plants, exerts its therapeutic effects through the modulation of various signaling pathways. Key pathways include the PI3K/AKT pathway, which is crucial for cell survival and proliferation, and the NF-κB pathway, which plays a significant role in inflammation and immune responses. Phytochemicals from plants have been shown to modulate these pathways effectively, thereby controlling macrophage biology and influencing the balance between pro-inflammatory (M1) and anti-inflammatory (M2) macrophage phenotypes.

The regulation of gene expression by phytochemicals involves epigenetic modifications such as histone modification, DNA methylation, and miRNA-mediated post-transcriptional changes. These modifications can either induce or suppress inflammatory signaling, thereby maintaining immune homeostasis and preventing chronic inflammation. Phytochemicals have been identified to target these epigenetic mechanisms, thereby attenuating aberrant inflammation and potentially reducing the risk of inflammation-mediated diseases (Ahmed et al., 2022).

Phytochemicals also impact cellular metabolism by modulating oxidative stress and enhancing antioxidant defenses. They achieve this by down-regulating reactive oxygen species (ROS) and up-regulating antioxidant enzymes like superoxide dismutase (SOD). This modulation helps in reducing oxidative stress, which is a key factor in chronic inflammation and various metabolic disorders (Houghton, 2019).

### 4.2 Interaction with biological pathways

*Hydrocotyle vulgaris* interacts with inflammatory pathways by modulating the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This modulation is achieved through the inhibition of key signaling molecules like NF-κB and MAPKs, which are central to the inflammatory response. By targeting these pathways, phytochemicals can effectively reduce inflammation and its associated symptoms (Figure 2) (Merecz-Sadowska et al., 2020; Shin et al., 2020).

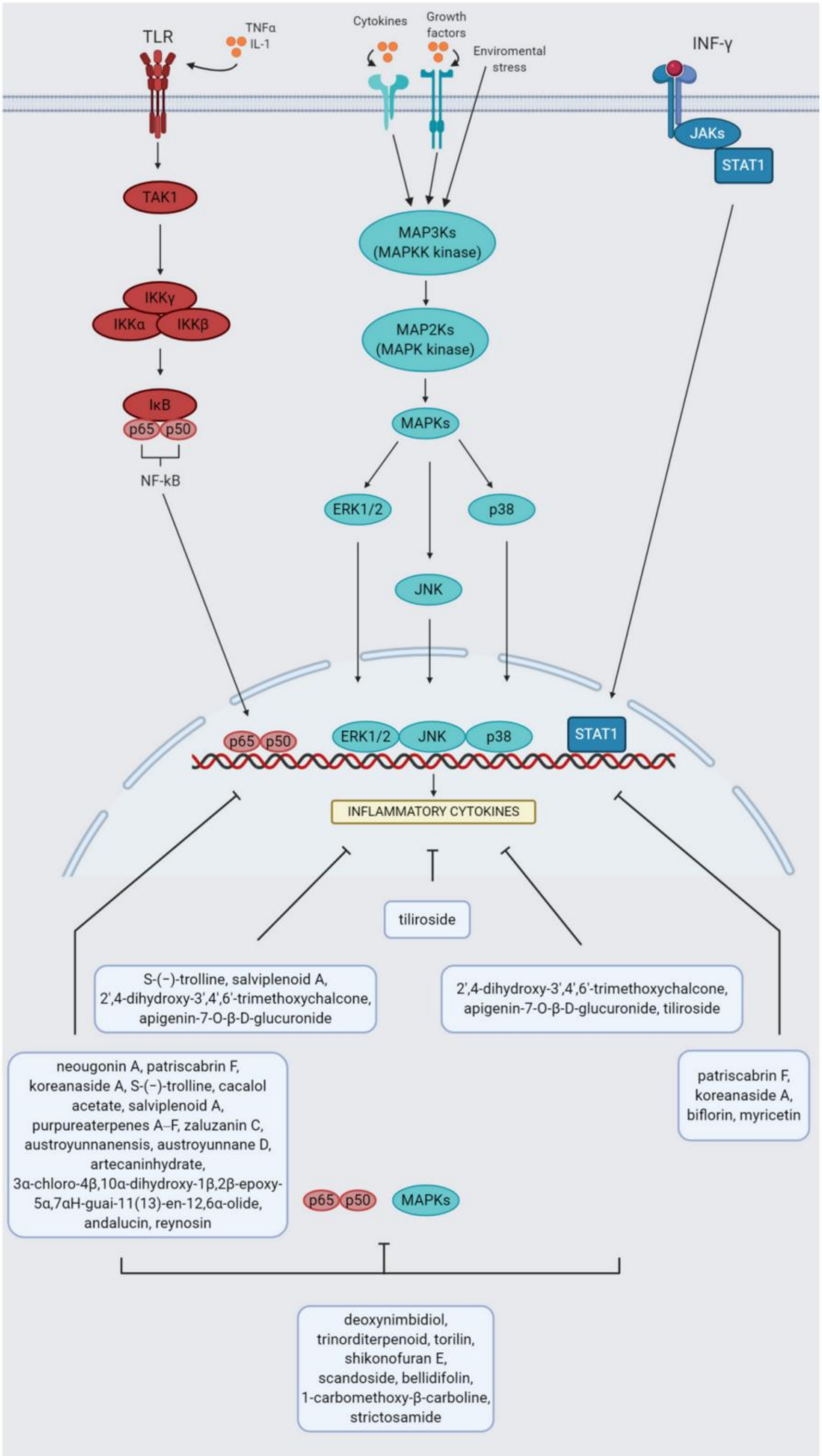


Figure 2 NF-κB, MAPKs, JAK/STAT1 pathways and plant-derived inhibitors (Adopted from Merecz-Sadowska et al., 2020)

The modulation of oxidative stress response by *Hydrocotyle vulgaris* involves the activation of antioxidant pathways and the reduction of oxidative stress markers like ROS and malondialdehyde (MDA). Phytochemicals enhance the body's antioxidant capacity by up-regulating enzymes such as SOD and catalase, thereby protecting cells from oxidative damage and reducing the risk of chronic diseases (Soleymani et al., 2019). Phytochemicals from *Hydrocotyle vulgaris* also play a role in immune system regulation by modulating the activity of immune cells such as macrophages and T-cells. They enhance innate and adaptive immune responses, thereby improving the body's ability to fight infections and reducing the risk of immune-related disorders. This immunomodulatory effect is crucial for maintaining overall health and preventing chronic inflammation (Gomes et al., 2019; Saleh et al., 2021).

### 4.3 Synergistic effects with other compounds

The therapeutic potential of *Hydrocotyle vulgaris* can be enhanced when combined with other herbal extracts. Synergistic effects have been observed when phytochemicals from different plants are used together, leading to improved efficacy in treating various conditions. This combination can enhance the bioavailability and potency of the active compounds, thereby providing better therapeutic outcomes (Ahmed et al., 2022).

While the combination of *Hydrocotyle vulgaris* with other herbs can be beneficial, it is also important to consider potential drug-herb interactions. Phytochemicals can interact with conventional drugs, either enhancing or inhibiting their effects. Therefore, careful consideration and monitoring are required when using *Hydrocotyle vulgaris* in conjunction with other medications to avoid adverse effects. The bioavailability of phytochemicals from *Hydrocotyle vulgaris* can be a limiting factor in their therapeutic efficacy. However, combining these phytochemicals with other compounds can enhance their absorption and bioavailability. Techniques such as the use of bioenhancers or formulation with other bioactive compounds can improve the delivery and effectiveness of these phytochemicals in the body (Houghton, 2019; Jantan et al., 2021).

## 5 Case Study

### 5.1 Historical uses in traditional medicine

*Hydrocotyle vulgaris*, commonly known as pennywort, has been utilized in various traditional medicine systems for centuries. Historically, it has been employed by different cultures for its purported therapeutic properties. For instance, in traditional Chinese medicine, a related species, *Hydrocotyle sibthorpioides*, has been used to treat a wide array of ailments including fever, edema, dysentery, and rheumatalgia. It has also been used as a brain tonic, detoxifying agent, and hepatoprotective agent (Hazarika et al., 2020). Similarly, in European folk medicine, plants like *Alchemilla vulgaris*, which share some phytochemical properties with *Hydrocotyle vulgaris*, have been used for their astringent and anti-inflammatory properties, particularly in the treatment of gynecological and gastrointestinal diseases.

### 5.2 Modern applications in healthcare

In contemporary healthcare, the therapeutic potential of *Hydrocotyle vulgaris* is being explored through scientific validation. Modern pharmacological studies have confirmed several traditional uses of related species. For example, *Hydrocotyle sibthorpioides* has demonstrated significant pharmacological activities such as cognitive enhancement, anti-cancer, antiviral, antibacterial, antifungal, and hepatoprotective effects. *Alchemilla vulgaris* has been scientifically validated for its wound healing potential, particularly when incorporated into hydrogels for topical application. This modern approach has shown that the plant's extracts can accelerate wound healing, attributed to their phenolic compounds, antioxidant activity, and favorable pH levels (Kong et al., 2023).

### 5.3 Comparative analysis of traditional and modern uses

A comparative analysis of the traditional and modern uses of *Hydrocotyle vulgaris* and related species reveals a significant overlap in their therapeutic applications. Traditional uses, such as the treatment of inflammatory conditions and wound healing, have been substantiated by modern pharmacological studies. For instance, the traditional use of *Hydrocotyle sibthorpioides* for treating infections and inflammation aligns with its scientifically proven antibacterial, antifungal, and anti-inflammatory properties (Hazarika et al., 2020). Similarly, the folkloric use of *Alchemilla vulgaris* in wound healing has been validated through in vitro and in vivo studies, demonstrating its efficacy in promoting skin repair (Tasić-Kostov et al., 2019). This convergence of traditional knowledge and modern science underscores the enduring value of these medicinal plants and highlights the importance of integrating traditional medicine with contemporary healthcare practices. By bridging the gap between historical uses and modern scientific validation, we can better understand the full therapeutic potential of *Hydrocotyle vulgaris* and related species, paving the way for their incorporation into modern medical treatments.

## 6 Safety and Toxicity

### 6.1 Assessment of toxicity levels

The assessment of toxicity levels in *Hydrocotyle vulgaris* has been explored through various studies focusing on its phytochemical properties and potential therapeutic applications. One study investigated the heavy metal content and phytochemical composition of a related species, *Hydrocotyle sibthorpioides*, and found negligible amounts of toxic elements, suggesting a low toxicity profile for the genus (Swargiary and Daimari, 2021). The study highlighted the plant's potential for safe use in medicinal applications due to its minimal toxic effects and high cell membrane permeability.

### 6.2 Safe dosage ranges

Determining safe dosage ranges for *Hydrocotyle vulgaris* involves evaluating its physiological responses under different conditions. For instance, a study on the plant's cadmium tolerance revealed that it could grow normally under various cadmium concentrations, indicating a robust tolerance to environmental stressors (Liu et al., 2021). This resilience suggests that *Hydrocotyle vulgaris* can be safely used within a broad range of dosages without adverse effects. However, specific dosage recommendations for therapeutic use would require further detailed pharmacological studies.

### 6.3 Long-term safety studies

Long-term safety studies are crucial to understanding the chronic effects of *Hydrocotyle vulgaris* consumption. While there is limited direct research on the long-term safety of *Hydrocotyle vulgaris*, insights can be drawn from studies on its antioxidant and free radical scavenging activities. For example, research has shown that *Hydrocotyle vulgaris* possesses significant antioxidant properties, which could mitigate oxidative stress and reduce the risk of long-term toxicity. Moreover, the plant's non-irritating pH levels and good spreadability values further support its potential for safe long-term use in biocosmetic applications (Ureta et al., 2018). Nonetheless, comprehensive long-term studies are necessary to fully establish its safety profile over extended periods.

## 7 Challenges and Future Directions

### 7.1 Current research limitations

Despite the promising therapeutic potential of *Hydrocotyle vulgaris*, current research has several limitations. One significant limitation is the lack of comprehensive clinical trials to validate the efficacy and safety of *H. vulgaris* in human subjects. Most studies, such as those evaluating its antioxidant properties and free radical scavenging activities, have been conducted in vitro or in animal models (Ureta et al., 2018). The variability in extraction methods and phytochemical analysis techniques can lead to inconsistent results, making it difficult to standardize the therapeutic use of *H. vulgaris*. There is limited information on the long-term effects and potential side effects of *H. vulgaris*, which is crucial for its integration into modern medicine.

### 7.2 Potential areas for future study

Future research should focus on several key areas to fully realize the therapeutic potential of *Hydrocotyle vulgaris*. Firstly, conducting well-designed clinical trials is essential to establish the efficacy and safety of *H. vulgaris* in treating various conditions, particularly those related to oxidative stress and aging. Exploring the plant's potential in phytoremediation, as indicated by its cadmium tolerance and removal efficiency, could open new avenues for environmental applications (Ni et al., 2018; García-Oliveira et al., 2021). Investigating the synergistic effects of *H. vulgaris* with other medicinal plants or conventional drugs could enhance its therapeutic efficacy. Research should also aim to standardize extraction and analysis methods to ensure consistency and reliability of results across different studies.

### 7.3 Integration into modern medicine

Integrating *Hydrocotyle vulgaris* into modern medicine requires a multifaceted approach. Establishing standardized protocols for its extraction, formulation, and dosage is crucial to ensure its therapeutic efficacy and safety. Collaboration between researchers, healthcare professionals, and regulatory bodies can facilitate the development of guidelines for its clinical use. Public awareness and education about the benefits and potential uses of *H. vulgaris* can promote its acceptance and integration into mainstream healthcare. Given its promising antioxidant and phytoremediation properties, *H. vulgaris* could be developed into biocosmetic products and environmental remediation solutions, respectively, thereby broadening its application scope (Ureta et al., 2018; Liu et al., 2021).

## 8 Concluding Remarks

*Hydrocotyle vulgaris* has demonstrated significant therapeutic potential through various studies. The plant exhibits strong free radical scavenging activity and antioxidant properties, which are crucial in combating oxidative stress and pathological aging. Key phytochemicals identified include flavonoids, alkaloids, and essential vitamins such as β-carotene, riboflavin, and vitamins C and E, which contribute to its therapeutic efficacy. Additionally, *H. vulgaris* has shown remarkable cadmium tolerance and phytoremediation capabilities, indicating its potential use in environmental cleanup efforts.

The antioxidant properties of *H. vulgaris* make it a promising candidate for developing biocosmetic products aimed at mitigating pathological aging. Its non-irritating pH levels and good spreadability further support its suitability for topical applications. Moreover, the plant's ability to tolerate and remediate cadmium-contaminated environments suggests potential applications in reducing heavy metal toxicity in affected areas, which could indirectly benefit human health by improving environmental conditions.

Future research on *Hydrocotyle vulgaris* should focus on exploring its full range of phytochemicals and their specific mechanisms of action. Investigating its potential in other therapeutic areas, such as wound healing and anti-inflammatory applications, could provide additional insights into its medicinal value. Furthermore, large-scale studies and clinical trials are necessary to validate its efficacy and safety for human use. Given its extensive habitat distribution and promising initial findings, *H. vulgaris* holds significant potential for both medical and environmental applications, warranting further scientific exploration.

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### Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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