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The Therapeutic Potential of HMs in Acute Gouty Arthritis Through Immune Regulation

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Abstract

Acute gouty arthritis (AGA) is marked by a swift inflammatory response triggered by the accumulation of monosodium urate (MSU) crystals around the joints, often linked to hyperuricemia (HUA). Traditional approaches in AGA management usually prove inadequate, prompting a recent focus on the potential of herbal medicines (HMs) for AGA treatment. This review aims to outline the pharmacological mechanisms of HMs in treating AGA, exploring their active components, extracts, and prescriptions, and discussing relevant molecular targets extensively. Scientific publications on anti-AGA HMs were gathered from diverse journals and databases like PubMed, Elsevier, and Google Scholar. The review identified numerous therapeutic targets for AGA treated by HMs through in vitro and in vivo studies. HMs and their active ingredients were found to alleviate AGA symptoms by influencing various immune cell targets. The study revealed that HMs have multiple therapeutic targets that effectively address AGA symptoms through in vitro and in vivo studies. The review systematically categorized the anti-AGA properties of HMs, highlighting phenolic, flavonoid, terpenoid, and alkaloid compounds as key ingredients for AGA improvement. HMs and their active ingredients are shown to enhance efficacy by interacting with multiple targets, with NLRP3 being a primary therapeutic focus. Further research is needed to fully understand how HMs alleviate AGA due to the complex nature of HMs.

Keywords: *Acute Gouty Arthritis, Herbal Medicines, Monosodium Urate Crystals, Pharmacological Mechanisms.*

Introduction

Gout, a type of autoimmune arthritis, arises from the build-up of MSU crystals in joints and tissues due to disruptions in purine metabolism [1]. The prevalence of this condition varies by geographical region, with higher rates observed in Europe and America compared to China [2]. The clinical advancement of gout consists of four stages: asymptomatic, crystal deposition, acute attack, and the development of chronic arthritis, with manifestations such as joint inflammation, swelling, and intense pain [3]. Resistant gout manifests as gout stones, joint impairment, and additional complications such as kidney disease and diabetes, associated with risk factors like genetics, age, gender, and diet. The pathogenesis entails the interaction of MSU with the local milieu, leading to inflammation through the involvement of macrophages, neutrophils, and T lymphocytes, activation of the NLRP3 inflammasome, and excessive production of proinflammatory cytokines. Initial treatments for acute gout episodes encompass NSAIDs, colchicine, and glucocorticoids, although their effectiveness might be hindered by adverse effects such as

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hepatorenal toxicity and gastrointestinal reactions [4].

In recent times, drug-targeted therapy has gained importance in treating AGA, utilizing IL-1β inhibitors and NLRP3-blocking biological drugs. However, challenges persist due to infection risks, immune response activation, and the high costs of orthodox drugs [5]. To address these issues, there is a pressing need for safer, more affordable drugs for AGA treatment [6]. HMs containing bioactive components like flavonoids and alkaloids show promise in managing [7]. AGA by targeting immune regulation, inflammation, and oxidative stress, warranting further exploration in ethnopharmacological studies for comprehensive understanding. This review aims to analyze the pharmacological mechanisms of traditional HMs in combating AGA, offering a valuable resource for exploring new treatment strategies.

The Therapeutic Potential of Targeting Immune Cells in the Treatment of AGA

Gout is currently acknowledged as a conventional inflammatory disorder that arises from the activation of the innate immune system, a finding widely accepted in contemporary medical literature. The participation of various types of immune cells, such as monocytes/macrophages, neutrophils, and lymphocytes, is deemed essential in the progression of the acute phase of gout, a fact that has been thoroughly explored and meticulously documented, instilling confidence in the accuracy of the information presented [8]. Macrophages, being among the earliest identified and extensively researched immune cells, have been found to exhibit apparent polarization in both acute and chronic gout, thereby assuming a critical role in orchestrating the entire trajectory of an acute gouty episode. This pivotal aspect has been extensively documented in scholarly works. The inflammatory response causes a significant increase in neutrophils in the synovium and synovial fluid, emphasizing their essential role in triggering gouty inflammation. This phenomenon has been the subject of intense investigation in the scientific community [5]. While the conventional understanding has long held that macrophages and neutrophils are the primary immune cells implicated in gout, recent studies have shed light on a significant correlation between specific subsets of T cells and Gouty Arthritis (GA), broadening our comprehension of the immunological landscape of this medical condition. Such T cell subsets encompass regulatory T cells, helper T cells, and natural killer T (NKT) cells, all of which are increasingly recognized as pivotal players in the pathophysiology of GA [9]. This concept has gained traction in recent scientific discourse. As the exploration into the pathogenesis of GA progresses, substantial strides have been achieved in therapeutic interventions targeting immune cells, marking a significant milestone in the quest for more effective treatment modalities for this debilitating ailment. This development holds promise for improving patient outcomes and quality of life shortly.

Role of Macrophage Polarization in Acute Gout

Macrophages, as pivotal effector cells within the body's innate immune system, play a central role in orchestrating the entire process of acute gout (AG). Their responsibility in initiating an acute gout attack is closely linked to the engulfment of monosodium urate (MSU) crystals through a process known as phagocytosis [10]. This process is facilitated by the recognition and ingestion of the deposited MSU crystals using Toll-like receptor2 (TLR2) and Toll-like receptor4 (TLR4) [11]. The transformation of macrophages into M1 macrophages is a critical step in initiating acute gouty arthritis (AGA), particularly during the phase of acute inflammation associated with the disease. Exposure to MSU crystals prompts macrophages to differentiate into M1

macrophages, while monocyte macrophages migrating from the peripheral blood can also undergo this differentiation process [12]. The release of inflammatory mediators like interleukin-1β (IL-1β) and interleukin-18 (IL-18) enhances the inflammatory response, thereby escalating the inflammation and facilitating its occurrence within the joint space. As the inflammatory process subsides, a shift towards M2 polarization becomes predominant, leading to the secretion of factors that dampen inflammation and suppress the inflammatory reaction. The transition of macrophages from M1 to M2 polarization is believed to play a role in limiting acute inflammation. In contrast, any disruption in this polarization process can result in the persistence of chronic acute inflammation [5]. The polarization of macrophages between the pro-inflammatory M1 and anti-inflammatory M2 phenotypes is critical in various conditions such as tissue repair, tumour progression, and infection management. In gout, characterized by monosodium urate (MSU) crystal deposition in joints, M1 macrophages drive inflammation, while M2 macrophages are involved in resolving inflammation and promoting tissue repair. The polarization of macrophages emerges as a critical factor in regulating acute inflammation in cases of gout. Consequently, within acute gout, different subtypes of macrophages are currently regarded as one of the primary targets for therapeutic intervention. The development of drugs that target macrophage apoptosis, inflammation, and polarization has become essential in the therapeutic strategy for managing acute gouty arthritis (AGA) [5,10].

Immunological Insights and Therapeutic Targets in Acute Gouty Arthritis

The significance of neutrophils in the management of AGA is multifaceted and complex. It is well-established that neutrophils play a crucial role in triggering and sustaining gouty inflammation; however, their involvement also encompasses anti-inflammatory functions through the release of neutrophil extracellular traps (NETs) during acute inflammation [13, 14]. Under normal circumstances, neutrophils are typically not found in the synovial fluid within joints; nevertheless, neutrophils infiltrate the inflamed joint regions in AGA scenarios. Given their essential role in the innate immune system, the recruitment and activation of neutrophils are fundamental in the acute inflammatory response to MSU crystals [14]. This process can lead to synovitis, localized joint damage, and systemic inflammation due to the secretion of various inflammatory mediators such as cytokines, chemokines, reactive oxygen species (ROS), and proteases. As the inflammatory cascade advances, numerous MSU crystals can attract many neutrophils, prompting the formation of extensive NETs known as neutrophil extracellular trap NETs (AggNETs) possessing proteolytic properties [14,15]. AggNETs can capture and enzymatically break down cytokines and chemokines derived from neutrophils, thus mitigating the inflammatory response. Consequently, therapeutic strategies aimed at neutrophils in AGA predominantly revolve around regulating the generation of NETs and promoting neutrophil apoptosis [14]. Presently, there is a scarcity of targeted therapies specifically tailored for neutrophils in AGA; nevertheless, this area shows promise as a potential novel therapeutic approach for treating this condition.

Recent research has brought to light functional irregularities in different T cell subgroups and abnormal cytokine expression in Gouty Arthritis (GA), leading to a shift in focus toward targeting T cells in treating AGA. The participation of T helper cell subgroups like T helper cell 1 (Th1), T helper cell 2 (Th2), T helper cell 17 (Th17), and regulatory T (Treg) cells has been acknowledged, along with macrophages and neutrophils [17]. It is widely recognized that maintaining a delicate equilibrium between Th1/Th2 and Th17/Treg

immune responses is vital for immune stability. The immune response amplification facilitated by Th1 and Th17 during the progression of AGA is considered crucial in initiating pro-inflammatory assaults. Clinical findings have indicated a continual variability in the Th1/Th2 equilibrium throughout the development of GA [19]. Individuals with AGA exhibit notably heightened levels of Th17 in comparison to those with borderline GA and individuals in good health, suggesting a potential involvement of Th17 in the inflammatory sequence of GA. The escalated Th17/Treg ratio is linked to the inflammatory progression of GA, indicating a connection between an unbalanced Th17/Treg ratio and the origin of the illness. As a result, preserving the balance between Th17 and Treg cells has emerged as a promising therapeutic strategy for AGA. Various flavonoids and alkaloids have demonstrated effectiveness in regulating the balance of T cells in both experimental models and clinical environments, underscoring their potential in managing AGA. These compounds act by modulating the immune response, thereby reducing inflammation and potentially slowing the progression of AGA [18].

NK cells, essential effector cells in innate immunity, are renowned for their prompt reaction to cellular stress or infection using cytotoxicity and cytokine production [19, 20]. These NK cells are comprised of two functional subsets: the CD56dim population, characterized by higher maturity and cytotoxicity, and the CD56bright NK cells, which exhibit lower cytotoxicity yet possess the ability to generate a substantial quantity of cytokines. Within acute gout, an elevation in the CD56bright NK cell population has been detected in the joints of affected individuals, suggesting the capacity of these cells to produce both pro-inflammatory and anti-inflammatory cytokines [19]. The critical involvement of monocytes/macrophages in the initial phases of gout is firmly established, with documented interactions between NK cells and these monocytes/macrophages. Moreover, NK cells can release anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). Evidence shows that they can modulate the activity of pro-inflammatory monocytes by eliminating highly active cells. These findings indicate that acute gout arthritis (AGA) represents an inflammatory state where NK cells could exert an immunomodulatory influence. Despite the absence of current therapies specifically targeting NK cells in AGA treatment, the potential of therapeutic approaches centred on NK cells introduces an innovative strategy for managing this condition [21]. In the forthcoming period, investigating interventions that regulate NK cell function in AGA might unveil fresh opportunities for implementing intervention strategies.

Therapeutic Role of HMs in AGA through Immune Regulation

Due to a wide array of bioactive phytochemicals and molecular targets within them, HMs exhibit a potent therapeutic effect that goes beyond the capabilities of specific traditional treatments [7, 22]. Numerous investigations carried out in both controlled laboratory environments and within living organisms have conclusively established that HM extract possesses the potential to exert a therapeutic influence against AGA by interacting with multiple targets simultaneously [7,9,18]. The scientific community's identification of macrophages as a novel and promising treatment approach has attracted considerable attention [5]. Extensive research conducted in animal subjects and in vitro studies has illustrated that the collective saponins present in *Dioscorea nipponica* can effectively alleviate symptoms associated with GA in rats [23]. The modulation of M1/M2 polarization in monocytes and macrophages, which is influenced by arachidonic acid signalling, is the mechanism through which this therapeutic effect is realized; the extracts can impede initial signalling cascades, thereby

affecting the NLRP3 inflammasome. For instance, the total glucosides of Paeonia (TGP) have been shown to mitigate inflammation in THP-1 macrophages induced by MSU by regulating the MALAT1/miR-876-5p/NLRP3 axis [24]. Studies have indicated that corilagin can alleviate joint inflammation caused by MSU crystals, suppress IL-1β production, and reduce the migration of macrophages and neutrophils toward the joint capsule [25]. This process may involve regulating the ROS/TXNIP/NLRP3 pathway, inhibiting NLRP3 inflammasome activation and pyroptosis, and attenuating inflammatory processes. Gallic acid, a phenolic compound commonly present in various plants, vegetables, nuts, and fruits, is notable for its anti-inflammatory and antioxidant properties [26]. Experiments conducted both in laboratory settings and in live organisms have highlighted the capacity of gallic acid to upregulate Nrf2 expression, diminish mtROS generation, inhibit the activation of NLRP3 inflammasome and pyroptosis, and reduce IL-1β levels in macrophages, thereby contributing to the alleviation of gout arthritis induced by MSU [25].

Cardamonin, predominantly found within the Zingiberaceae family, exhibits a broad spectrum of biological properties encompassing anticancer, anti-inflammatory, antioxidant, antiviral, antifungal, and antiallergic attributes [27]. Recent investigations have highlighted the potential of cardamonin as a promising intervention for chondrocyte inflammation and arthritis prevention. Experimental evidence indicates that cardamonin can reduce caspase-1 activity and suppress IL-1β secretion in J774A.1 macrophage following MSU stimulation [28]. Moreover, it has been demonstrated to mitigate the inner synovial layer thickness and infiltration in an in vivo GA model [29]. Baeckein E (BF-2), derived from *Baeckea frutescens* L., shows various biological effects. This particular compound has been historically utilized in ancient Southeast Asian medicine for its efficacy in addressing inflammatory conditions. BF-2 notably diminishes macrophage pyroptosis and IL-1β secretion induced by lipopolysaccharide, while alleviating ankle swelling in a gout mouse model. Further research indicates that BF-2 operates by obstructing the MAPK/NF-κB signalling pathway and reducing oxidative stress stemming from mitochondrial damage, ultimately impeding NLRP3 activation [30]. ALA directly inhibits the NAHT domain of NLRP3 to attenuate NLRP3 inflammasome activity. Studies involving acute lung injury and genetically modified mice demonstrate that ALA effectively hinders NLRP3 inflammasome activation in macrophages, thus preventing NLRP3-related diseases in living organisms [7].

TCM Compounds for Acute Gouty Arthritis: Mechanisms and Therapeutic Potential

Berberine (BBR), an isoquinoline alkaloid compound derived from various medicinal plants and widely utilized in Traditional Chinese Medicine, is renowned for its diverse biological and pharmacological effects, particularly its capacity to mitigate inflammation and modulate the immune response [31]. BBR has been shown to suppress pro-inflammatory responses in macrophages by stimulating AMPK and activating the Nrf2 transcription factor. This compound can alleviate AGA by suppressing inflammatory mediators and activating the Nrf2 antioxidant pathway. The Simiao pill, akin to Simiao decoction, is a traditional Chinese medicinal formula commonly employed in HM clinical settings for AGA treatment. Researchers have observed that the Simiao pill aids in reducing sodium urate crystal-induced arthritis in rats by promoting M2 polarization of macrophages [31]. Additionally, investigations have revealed that Simiao powder, when formulated similarly, can exacerbate MSU-induced gouty arthritis

while reducing hyperuricemia. Further research has unveiled that the anti-inflammatory properties of this substance can promote M2 macrophage polarization via the PI3K/Akt pathway, thereby contributing to its anti-inflammatory efficacy [32].

Corilagin, a type of Gallic tannin, is the primary active component found in Longan, *Phyllanthus urinaria* L, *Phyllanthus emblica* Linn, and other medicinal plants. Renowned for its exceptional antioxidant and anti-inflammatory properties, this compound is widely utilized in clinical settings to manage chronic liver disease, hepatitis B virus, rheumatoid arthritis, and other medical conditions. This unique structure underpins its diverse pharmacological activities, including antioxidative, anti-inflammatory, and anti-tumor properties. Corilagin has shown significant protective effects in various pathological conditions. Research studies have demonstrated that corilagin can alleviate joint swelling induced by MSU crystals and its capacity to suppress IL-1β levels and hinder the migration of macrophages and neutrophils toward the joint capsule. This modulation of inflammatory responses may be attributed to its regulation of the ROS/TXNIP/NLRP3 pathway, its inhibition of NLRP3 inflammasome activation and pyroptosis, and its anti-inflammatory effects. Additionally, luteolin has been shown to significantly diminish neutrophil infiltration, decrease the production of pro-inflammatory cytokines, and reduce oxidative stress in inflammation triggered by MSU crystals. Another investigation highlighted the potential of tanshinone IIA in ameliorating MSU-induced inflammation in AGA by targeting the NLRP3 inflammasome and neutrophil activity. Moreover, the Guizhi-Shaoyao-Zhimu Decoction (GSZD) stands as a classic Traditional Chinese Medicine (TCM) formula comprising ingredients such as cinnamon, peony, liquorice, ephedra, dried ginger, *Atractylodes macrocephala*, *Anemarrhena Rhizoma*, radix sileris, Aconitum, and other HMs components. Empirically utilized in HMs clinical practice for managing various forms of arthritis, GSZD has been subject to in vivo investigations showing significant reductions in neutrophil recruitment and levels of IL-1β, IL-6, and MCP-1 in peritoneal exudates of MIP mice [33-35]. The efficacy of GSZD against GA is associated with its ability to inhibit NFκB and NLRP3 inflammasome activation through the MAPK signalling pathway (Figure 1) [35].

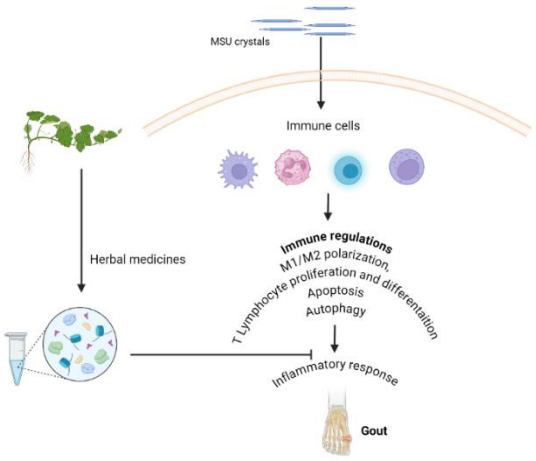

Figure 1. Therapeutic Role of HMs in AGA through Immune Regulation

Challenges and Future Directions

Gout, a condition stemming from the deposition of urate due to abnormal purine metabolism, can lead to severe inflammation, pain, and joint damage if left unaddressed. The complications that may arise if this ailment is left unaddressed can be severe. Herbal remedies have exhibited notable efficacy in managing gout through their targeted approach towards inflammation and immune system equilibrium. The potential of herbal remedies is truly inspiring. Recent advancements have highlighted new avenues for leveraging HMs to treat gout, including the potential targeting of IL-17 signalling and SHP2, which have displayed encouraging outcomes in managing interconnected conditions. There is a pressing need to delve further into the intricate composition of herbal remedies to unravel the active constituents and comprehensively comprehend their pharmacological actions. Cutting-edge methodologies like proteomics and single-cell sequencing hold significant promise in identifying novel therapeutic targets within HMs. The execution of clinical trials utilizing components of herbal remedies identified through randomized Controlled Trials could play a pivotal role in bridging the gap between scientific exploration and practical application in a clinical setting. Establishing a comprehensive information hub dedicated to AGAs-related diseases and syndromes emerges as a critical imperative for facilitating personalized and precisely targeted interventions for gout using herbal remedies. The potential of integrating contemporary medical frameworks with traditional HM practices has the potential to usher in a more efficacious and holistic approach to managing gout.

Conclusion

This review article provides a detailed examination of the pharmacological properties of active compounds in HMs formulations, focusing on their anti-AGA effects by targeting immune cells. Research highlights the diverse components and mechanisms of HMs, which contribute to their synergistic effects and promising results in combating AGA compared to conventional pharmaceuticals. This diversity is intriguing and should pique the interest of the audience.

Conflict of Interest

None

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Credit Authorship Contribution Statement

Malairaj Sathuvan: Conceptualization, Writing-original draft, Writing- review and editing

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