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Review Article

Hyperuricemia: Current State and Prospects

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Abstract

Hyperuricemia (HU), characterized by elevated uric acid (UA) levels in the blood, is a global health concern associated with various conditions, including cardiovascular diseases, gout, hypertension, metabolic syndrome, renal dysfunction, and neurodegenerative diseases. Recent studies highlight the multifaceted origins of HU, implicating genetic predisposition, dietary patterns, lifestyle choices, and environmental influences. Genetic variations affecting enzymes and transporters involved in purine metabolism and UA excretion have been identified, paving the way for personalized treatment strategies. Advances in diagnostic imaging and omics technologies provide enhanced precision in detecting and evaluating risks. While pharmacological interventions remain central to managing HU, persistent challenges such as treatment resistance necessitate the exploration of novel drug targets and lifestyle modifications. Chinese herbal medicines present a potential alternative with fewer side effects. Emerging research on the impact of gut microbiota on UA metabolism opens new therapeutic avenues. Despite progress, challenges such as optimizing treatment duration and understanding long-term effects remain. Collaborative efforts are essential to address these challenges and advance our comprehension of HU. Integrating precision medicine and holistic patient care approaches holds promise for improving outcomes and enhancing the quality of life for individuals with HU. This review provided a contemporary analysis of HU, covering its causes, associated health risks, diagnosis, treatment, and future outlook.

Introduction

Hyperuricemia (HU), a metabolic disorder characterized by elevated levels of uric acid (UA) in the bloodstream, is a significant global health concern. Generally, HU is diagnosed when UA levels exceed 420 μmol L^{-1} (7 mg/dL) for men and 350 μmol L^{-1} (6 mg/dL) for women, typically surpassing 7.0 mg/dL. Unlike many mammals, humans lack the enzyme uricase, which degrades UA to the more soluble compound allantoin. This deficiency results in UA levels approaching the theoretical limit of solubility in the serum (6.8 mg/dL).[1] HU can be induced by consuming purine-rich foods, cell breakdown, genetic factors, impaired kidney function, obesity, certain medications, metabolic diseases, alcohol consumption, and dehydration. The etiologies of HU can be acute, such as acute renal failure, cell lysis syndromes, and rhabdomyolysis, or chronic, such as genetic or iatrogenic origins. This condition is associated with numerous health complications, including cardiovascular diseases (CVDs), hypertension, gout, metabolic diseases, renal dysfunction,[2] and hearing impairment.[3] The pharmacological treatment of asymptomatic HU was not addressed in the American College of Rheumatology guidelines for managing gout or the European Alliance of Associations for Rheumatology's evidence-based recommendations for gout.[4,5] However, the guidelines from the Japanese Society of Hypertension and the Japanese Society of Gout and Nucleic Acid Metabolism recommend managing HU, although this management is often insufficient.[6] In China, there is also a positive attitude toward treating HU.[7] As our understanding of HU deepens, it becomes increasingly evident that its etiology is multifactorial, stemming from a complex interplay of genetic predisposition, dietary habits, lifestyle choices, and environmental factors.[2,8,9]

Fundamentally, HU manifests when the balance between UA production and excretion is disrupted. UA production primarily occurs through the metabolism of purine nucleotides, with dietary purines contributing significantly to this process.[8] Figure 1 illustrates a simplified UA metabolism pathway, highlighting the key enzymes involved. Genetic factors play a crucial role in predisposing individuals to HU.[10] Variations in genes encoding UA transporters, such as *SLC2A9* and *ABCG2*, can influence UA levels by affecting renal reabsorption and secretion.[11] Furthermore, polymorphisms in enzymes involved in purine metabolism, such as xanthine oxidase (XO),[12] may contribute to increased UA production. Environmental factors, including exposure to heavy metals, can interfere with UA excretion by damaging renal tissue cells.[13] The intricate relationship between genetic predisposition and environmental influences highlights the multifaceted nature of HU.

Due to current controversies and less-than-ideal treatment out-

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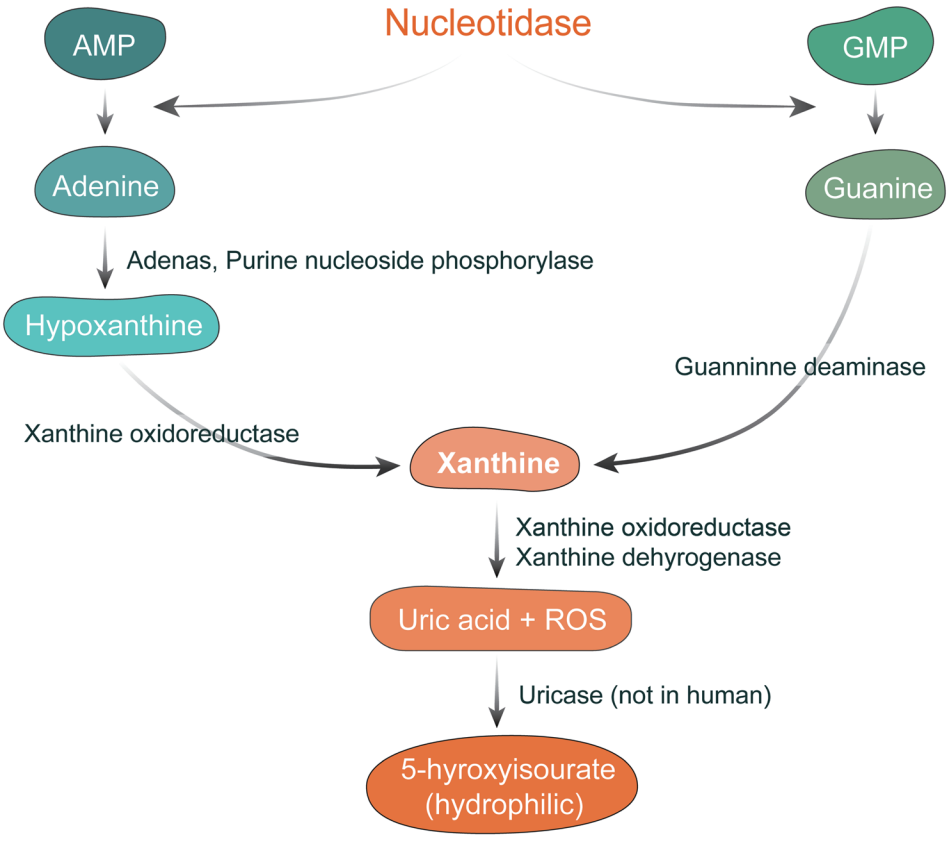

Fig. 1. The simplified uric acid metabolic pathways. The main enzymes play crucial roles in predisposing individuals to hyperuricemia. AMP, adenosine monophosphate; GMP, guanosine monophosphate; ROS, reactive oxygen species.

comes in the management of HU worldwide, evolving discoveries have drawn attention to its role in various pathologies. Timely consolidation and integration of findings will facilitate effective treatment for individuals with HU and aid clinicians in providing better care. This review offers a contemporary analysis of the current state of understanding HU, its underlying causes, associated health risks, diagnostic approaches, treatment strategies, and prospects for future research and management.

Association with health risks

The consequences of untreated HU extend beyond the biochemical abnormalities associated with elevated UA levels. CVDs are among the most concerning complications of HU, with numerous studies linking high UA levels to an increased risk of coronary artery disease, hypertension, metabolic syndrome (MS), and stroke.[14] Endothelial dysfunction, oxidative stress, inflammation, and activation of the renin-angiotensin-aldosterone system have been proposed as potential mechanisms underlying the cardiovascular effects of HU.[15] HU can exacerbate endothelial cell pyroptosis within aortic atherosclerotic plaques, advancing the progression of atherosclerosis.[16] Furthermore, elevated levels of soluble UA can initiate the activation of the nucleotide-binding oligomerization domain (NOD)-, Leucine-rich repeat (LRR)- and pyrin domain-containing protein 3 inflammasome,[17] leading to endothelial cell pyroptosis, a process modulated by cellular levels of reactive oxidative species. Gout, a painful arthritic condition caused by the deposition of urate crystals in joints, is one of the most widely recognized consequences of elevated UA levels. Although not all HU patients will experience gout flares, HU is a primary risk factor for gout, and both conditions lead to systemic metabolic alterations underlying metabolic disorders.[18] The association between HU and various health risks has been extensively researched. Understanding these mechanisms is crucial for implementing targeted interventions aimed at reducing cardiovascular and other risks in individuals with HU.

Gout, a form of inflammatory arthritis, is perhaps the most recognizable consequence of HU. The deposition of urate crystals in the joints triggers acute episodes of intense pain, swelling, and inflammation characteristic of gouty arthritis.[2] Recurrent gout attacks not only cause significant morbidity but can also lead to joint damage and deformity if left untreated. Moreover, chronic HU has been implicated in the development of tophi, urate crystal deposits that can form in soft tissues surrounding the joints, further complicating the management of gout.

The association of HU with CVD has been debated over the last few decades. Most recent studies show a strong correlation between HU and CVDs, despite the cut-off of damaging levels of UA not being firmly established.[14] However, whether treating HU could reduce cardiovascular events is still inconclusive.[19] HU has also been associated with an increased risk of developing hypertension, and a chronic phase of microvascular injury is known to occur after prolonged periods of HU.[20]

MS is correlated with HU, with approximately one-third of patients with MS also presenting with HU.[21] HU is emerging as a

potential biomarker for MS and its constellations of obesity, hyperglycemia, hypertension, and dyslipidemia. The key molecules of these conditions, including the insulin receptor, glucose transporter type 4, cationic amino acid transporter-1, endothelial nitric oxide synthase, glycoprotein IV, and UA transporters, are located on the cell surface domain of caveolae, fulfilling their functions.[2,22] Any disruption reducing the number of caveolae on the cell surface can concurrently manifest MS and HU.

HU is also an independent risk factor for renal insufficiency and acute kidney injury in septic patients.[23,24] Renal dysfunction is both a cause and consequence of HU, creating a vicious cycle that exacerbates the condition's severity.[25] Chronic kidney disease impairs UA excretion, leading to further elevations in serum UA levels. Conversely, HU has been implicated in the progression of renal disease through mechanisms such as tubulointerstitial inflammation, oxidative stress, and endothelial dysfunction. The evidence suggests that asymptomatic HU is likely injurious, particularly in subgroups with renal conditions, systemic crystal deposits, frequent urinary crystalluria or kidney stones, and high intracellular UA levels.[26] Managing HU in patients with renal impairment poses unique challenges, emphasizing the importance of early detection and intervention to mitigate renal complications.

Although low levels of plasma UA may detrimentally affect cognitive function,[27] patients with HU or gout might have a decreased risk of neurodegenerative diseases (such as Alzheimer's disease and dementia) and an increased risk of cerebrovascular disease.[28] The neuroprotective or antioxidant roles of UA in pathogenesis still require confirmation.

Recent advances in genomics have shed light on the genetic factors contributing to HU.[10] Genetic variants associated with enzymes involved in purine metabolism and UA excretion have been identified. Understanding these genetic markers allows for a more personalized approach to treatment. Precision medicine, which involves tailoring therapeutic interventions based on an individual's genetic makeup, has the potential to revolutionize HU management. By identifying genetic predispositions, clinicians can develop targeted strategies that address the root causes of HU, optimizing treatment outcomes. Over the last decade, genome-wide association studies have pinpointed numerous genetic variants, predominantly single nucleotide polymorphisms, linked to HU. These polymorphisms offer a continuous measure of genetic susceptibility, aiding in the assessment of HU development risk. Genetic variants of inflammasome genes and their molecular partners may influence HU and gout susceptibility. Notably, a newly identified UA binding protein, the neuronal apoptosis inhibitor protein, is proposed to play a role in the paradox of asymptomatic HU.[29] Neuronal apoptosis inhibitor protein is a potential molecule for UA recognition and a sensor for NOD-, LRR- and pyrin domain-containing protein 3 and nucleotide-binding leucine-rich repeat receptor (NLR) family caspase activation and recruitment domain-containing 4 inflammasomes. UA may serve as the endogenous ligand involved in activating inflammatory and immunological pathways, playing a role in both pro-inflammatory and neuroprotective environments.[29]

HU represents a multifaceted metabolic disorder with far-reaching implications for health and well-being. Its intricate pathogenesis involves a combination of genetic predisposition, dietary factors, lifestyle choices, and environmental influences. Recognizing HU as a risk factor for CVDs, gout, and renal dysfunction underscores the importance of proactive management strategies aimed at reducing UA levels and mitigating associated complications. By addressing the underlying causes and implementing targeted interventions, healthcare providers can improve outcomes and enhance the quality of life for individuals living with HU.

Current diagnostic approaches

Timely and accurate diagnosis is crucial for effectively managing HU. Serum UA measurement remains the primary diagnostic method, with elevated levels indicating HU. Despite the discovery of some metabolic profile variations between HU and gout,[9,30] the search for biomarkers of HU is not prioritized due to its straightforward definition. However, reprogramming *E. coli* has emerged as a potential synthetic biology therapy for monitoring serum UA levels.[31] Additionally, other contributing factors or coexisting conditions may need to be assessed, as increased serum UA levels with immunosuppression could contribute to the coexistence of HU or gout in patients with systemic inflammatory disorders receiving effective therapies.[32] Technological advancements have improved diagnostic accuracy. Imaging techniques like ultrasound and dual-energy computed tomography offer non-invasive visualization of urate crystal deposits, aiding in both diagnosis and understanding their severity.[33] UA clearance, a calculated ratio based on blood and urine UA levels, may provide new insights into managing HU.[34] Identifying novel biomarkers associated with HU and its complications could lead to promising treatment strategies. Advanced omics technologies enable a comprehensive examination of molecular pathways, facilitating the identification of intervention targets. Integrating these biomarkers into clinical practice could revolutionize early detection and risk assessment, allowing for proactive and personalized management approaches.

Treatment strategies

Pharmacological interventions are integral to managing HU, especially when lifestyle modifications are insufficient. However, it is essential to carefully consider individual patient characteristics, comorbidities, and potential drug interactions when selecting medications. XO inhibitors like allopurinol and febuxostat are recommended as first-line treatments for HU, with uricosuric agents serving as second-line options. Combination therapy with both XO inhibitors and uricosuric agents is advised when monotherapy proves ineffective.[35] Despite the availability of various oral urate-lowering medications, treatment failure and refractory disease remain significant challenges. Newly developed drugs such as lesinurad, when used in conjunction with XO inhibitors, offer promising outcomes for patients with gout who haven't achieved target serum UA levels with XO inhibitors alone.[36] Interleukin-1 inhibitors have emerged as valuable additions to the treatment arsenal, particularly for refractory gout cases or patients with comorbidities.[35] These drugs effectively lower serum UA levels and prevent gout recurrence. Uricosuric agents like dotinurad enhance UA excretion by targeting specific enzymes involved in purine metabolism.[37] Anti-inflammatory agents are often co-administered with UA-lowering drugs. Ongoing research is focused on developing new uricosuric agents and investigating anti-inflammatory agents to improve HU management.[2]

While numerous UA-lowering agents demonstrate efficacy, their application is often limited by adverse effects. Traditional Chinese medicine (TCM) and edible plants have emerged as alternative treatments for HU.[38] Long-term clinical practice with TCM formulas has shown relative safety for short-term HU treatment.[39] TCM and natural products offer similar UA-lowering efficacy as Western medicine but with fewer adverse effects.[40] Various Chi-

nese herbs and formulas targeting heat clearance and dampness drainage have proven effective and safe for HU treatment. Modern pharmacological studies in animal models have confirmed the protective effects of TCM herbs on liver xanthine oxidoreductase activity and renal urate transporters, similar to commercial drugs.[40] The concomitant use of TCM for HU is gaining traction due to its ability to impact various signaling pathways and UA transporters, promoting balanced inflammatory interactions and UA excretion.[41] Natural products containing flavonoids, terpenoids, alkaloids, and other compounds show promise as urate transporter 1 or XO inhibitors.[42,43] Phytochemicals derived from natural sources possess the beneficial property of downregulating UA levels and dissolving monosodium urate crystals.[44] Specific TCM components like *Dendrobium officinale* exhibit anti-HU effects by regulating urate transport-related transporters and inhibiting XO activity.[45] Additionally, dietary patterns such as the Mediterranean and Dietary Approaches to Stop Hypertension diets play a role in reducing serum UA concentrations and preventing HU by influencing gut microbiota and purine metabolism directly or indirectly.[46]

Recent investigations have illuminated the potential engagement of gut microbiota in UA metabolism, unveiling new pathways for innovative interventions. Preliminary studies in animal models have yielded promising outcomes, indicating that interventions directed at the gut microbiota might modify UA metabolism. Probiotics have proven effective in alleviating HU by absorbing purines, restoring gut microbiota balance, and inhibiting XO activity.[46] Treatment with *Lactiplantibacillus plantarum* improves gut microbiota dysbiosis in hyperuricemic mice, reducing inflammation and HU-associated flora while promoting the production of short-chain fatty acids.[47] Conversely, the genus *Collinsella* may be the gut microbiota most directly linked to elevated blood uric acid levels.[48] Additionally, the depletion of microbiota in uricase-deficient mice has resulted in significant HU, while the administration of anaerobe-targeted antibiotics increases the risk of gout in humans.[49] Pharmaceutically restoring the probiotic uricolytic pathway represents a promising approach to efficiently converting urate to (S)-allantoin without intermediate metabolite accumulation for HU treatment.[50] Integration of FtsP-uricase into the genetically isolated region of probiotic *Escherichia coli Nissle* maintains probiotic traits and overall gene expression for HU treatment.[51] *Streptococcus thermophilus* IDCC 2201 effectively lowers UA levels by degrading purine nucleosides, restoring intestinal flora, and promoting short-chain fatty acid production, making it a potential adjuvant treatment for HU.[52] Enhancing enzymatic capacity for urate degradation via a genome-based insulated system may offer an optimal strategy for lowering UA levels. Treatment options for HU encompass XO inhibitors, uricosuric medications, and recombinant uricases.[53]

Prioritizing serum UA optimization is crucial, with lifestyle modifications and novel therapeutic approaches offering hope. Combining XO inhibitors and uricosuric agents may enhance treatment efficacy, while personalized medicine and innovative interventions show promise for future management. While lifestyle modifications can reduce serum UA levels, dietary changes alone may not adequately optimize serum UA levels, necessitating specific treatments.[35] The prospect of personalized medicine, tailoring treatment plans based on individual genetic and metabolic profiles,[54] holds promise for more effective and targeted management in the future.

Role of lifestyle factors

Various lifestyle factors, including sleep, exercise, dietary supplements, eating habits, and other behaviors, along with genetic predispositions, contribute to either UA overproduction or underexcretion, predisposing individuals to HU. Unfavorable habits such as excessive consumption of meat broth, seafood, fructose, and alcohol, as well as irregular or insufficient sleep and prolonged sedentary behavior,[55,56] may contribute to the onset of HU. Managing UA levels emphasizes the concept of "food as medicine," with dietary adjustments effectively controlling UA levels. Alkalization of urine by eating nutritionally well-designed food could be effective for removing UA from the body.[57,58] It's crucial to identify foods suitable for individuals with high UA levels and provide tailored meal plans and eating schedules. Despite purine-rich foods potentially raising UA levels,[8] especially in those with impaired UA clearance, excessive alcohol, and fructose-rich beverages have also been linked to HU.[10] Factors such as ethanol catabolism, lactic acid inhibition of renal urate excretion, acute liver damage, and fructose consumption affect the production of UA metabolic enzymes and UA transporters,[59] or intensify adenosine triphosphate degradation,[60] contributing to elevated serum UA levels following alcohol or fructose intake. Encouraging moderation in alcohol consumption and ensuring adequate hydration are essential aspects of HU management.

Regular physical activity aids in managing HU by promoting weight loss or maintenance,[61] which is crucial for reducing UA levels associated with excess body weight. Exercise improves insulin sensitivity, regulating glucose and lipid metabolism, thus potentially lowering UA levels. Enhanced blood circulation from exercise stimulates kidney function, promoting UA excretion through urine. Exercise increases blood shear stress, which can dynamically regulate UA transporters located on the cell surface domain of caveolae.[2,62] Additionally, exercise exhibits anti-inflammatory effects, reducing inflammation linked to HU and gout.[18] These combined benefits of exercise contribute to lower UA levels and decreased risk of gout attacks. However, it's worth noting that intense exercise may potentially reduce UA solubility by elevating lactate concentration,[63] induce dehydrated HU,[64] and increase the risk of rhabdomyolysis through the release of UA from skeletal muscle.[65] Therefore, consulting a healthcare professional before starting an exercise regimen is advised, especially for those with medical conditions.

Adopting a healthy lifestyle may partially mitigate the genetic predisposition to HU, with dietary factors playing a smaller but still significant role in serum urate variance and influencing the overall population risk.[66] Lifestyle modifications, including reducing purine-rich food intake, maintaining a healthy weight, and engaging in regular physical activity, are crucial for preventing or managing HU.[67] Additionally, promoting good sleep hygiene,[68] regular physical activity, and outdoor recreational activities can help individuals maintain normal UA levels.[61]

Future directions

Recent research has significantly broadened the therapeutic options for HU, focusing on novel drug targets and innovative approaches. Enzymes involved in purine metabolism, such as adenosine deaminase,[69] are being investigated as potential targets for drug development to regulate UA levels more effectively. Another promising avenue involves exploring anti-inflammatory agents for managing HU-related complications.[70] Inflammation plays a pivotal role in the pathogenesis of gout and other associated conditions. Investigating the use of anti-inflammatory medications such as colchicine and interleukin-1 inhibitors could provide additional benefits by reducing the frequency and severity of gout attacks.[71]

Recent studies have also highlighted the intricate relationship between gut microbiota and UA metabolism. The gut microbiome influences purine breakdown and the production of short-chain fatty acids, impacting UA levels. Modulating the gut microbiota through probiotics or fecal microbiota transplantation represents a novel approach to managing HU.[47] However, further research is necessary to establish the safety and efficacy of microbiota-targeted interventions in humans. Understanding the complex interplay between gut microbiota and HU opens avenues for innovative and personalized therapeutic strategies.

Precision medicine extends to lifestyle recommendations in managing HU. By understanding an individual's genetic predisposition to HU, personalized dietary advice can be provided, taking into account variations in purine metabolism. Tailoring lifestyle interventions based on genetic and metabolic profiles enhances their effectiveness and promotes long-term adherence. Genetic factors, lifestyle choices, and environmental influences contribute to the heterogeneity of HU presentation. Integrating individual patient data, including genetic information, into treatment decisions allows clinicians to optimize therapeutic outcomes. Genetic markers associated with HU susceptibility and drug response can guide treatment selection. For instance, certain genetic variants may affect the efficacy and safety of specific pharmacological agents.[72] Integrating genetic testing into the diagnostic process allows for a more nuanced understanding of the patient's risk profile and potential treatment responses.

Despite significant progress, challenges and unanswered questions persist in HU management. Determining the optimal duration of pharmacological interventions, potential long-term side effects, and the impact of HU management on cardiovascular outcomes requires further investigation. The complex interplay between genetics, environment, and lifestyle necessitates a holistic and personalized approach to patient care. Future research should focus on identifying additional genetic markers, refining diagnostic criteria, and elucidating the molecular pathways underlying HU-related complications. Large-scale prospective studies are essential to establish the long-term safety and efficacy of emerging therapies. Collaborative efforts among clinicians, researchers, and pharmaceutical industries will be pivotal in advancing our understanding and improving patient outcomes.

Conclusion

HU, with its complex interaction of genetic, lifestyle, and environmental factors, poses a multifaceted challenge in contemporary medicine. This comprehensive review provides an in-depth analysis of the current understanding of HU, encompassing its definition, causes, associated health risks, diagnostic approaches, treatment strategies, and future prospects. Advances in genomics, diagnostic imaging, and therapeutic options have significantly expanded our understanding and capabilities in managing HU. Precision medicine principles, which target individual genetic and metabolic profiles, show promise for more effective and personalized interventions. Emerging therapies such as microbiota-targeted interventions and anti-inflammatory agents present new avenues for future research and therapeutic development. As we navigate the complexities of HU, a holistic approach that considers the diverse factors influencing its development and progression is essential. Collaborative efforts among researchers, clinicians, and patients will drive further innovations, ultimately enhancing our ability to prevent, diagnose, and manage HU, thereby improving overall patient care.

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Conflict of interest

WZZ has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since 2024. The author declares no other conflicts of interest.

Author contributions

WZZ is the sole author of this manuscript.

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