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ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Suman Baral, MD, Assistant Professor, Department of Surgery, Mediplus Hospital and Trauma Center, Pokhara 33700, Nepal. brylsuman.sur@gmail.com

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LETTER TO THE EDITOR

Potential of traditional Chinese medicine lyophilized powder of *Poecilobdella manillensis* in the treatment of hyperuricemia

Kang-Ming Huang, Hong-Bin Chen, Jin-Rong Lin

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Kang-Ming Huang, Hong-Bin Chen, Department of Gastroenterology, Sanming First Affiliated Hospital of Fujian Medical University, Sanming 365000, Fujian Province, China

Jin-Rong Lin, Department of Ultrasound imaging, The First Affiliated Hospital of Xiamen University, Xiamen 361000, Fujian Province, China

Corresponding author: Hong-Bin Chen, BM BCh, Chief Physician, Department of Gastroenterology, Sanming First Affiliated Hospital of Fujian Medical University, No. 29 Liedong Street, Sanyuan District, Sanming 365000, Fujian Province, China. smchb2008@qq.com

Abstract

Traditional Chinese medicine has a long and illustrious history, and with the development of modern science and technology, the research and application of traditional Chinese medicines have continued to progress significantly. Many traditional Chinese medicinal herbs have undergone scientific validation, reinvigorating with new life and vitality, and contributing unique strengths to the advancement of human health. Recently, the discovery that leech total protein extracted from *Poecilobdella manillensis* lyophilized powder reduces blood uric acid (UA) levels by inhibiting the activity of xanthine oxidase to decrease UA synthesis and promotes UA excretion by regulating different UA transporters in the kidney and intestine has undoubtedly injected new vitality and hope into this field of research. The purpose of this editorial is to comment on this study, explore its strengths and weaknesses, and there is a hope to treat a range of metabolic-related syndromes, including hyperuricemia, by targeting the gut microbiota.

Key Words: Gut microbiota; Metabolism; Multi-omics; *Poecilobdella manillensis*; Sphingolipid metabolism pathway; Galactose metabolism pathway; Hyperuricemia

Core Tip: Currently, there are still many limitations in the therapeutic drugs for hyperuricemia (HUA), and the side effects of drugs significantly restrict their clinical application. The total leech total protein (LTP) extracted from the *Poecilobdella manillensis* lyophilized powder from traditional Chinese medicine can reduce blood uric acid through multiple targets and channels. This paper demonstrates that whole LTP will be an important addition to the treatment of HUA in the future, and is expected to further promote the study of the role of LTP on the regulation of the gut microbiota and the serum metabolome, and provide new insights into the therapeutic strategy of HUA.

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TO THE EDITOR

Hyperuricaemia (HUA) resulting from disorders of purine metabolism is a metabolic disease. Over the past few decades, the global incidence of HUA has escalated significantly, primarily attributed to the swift economic growth and the subsequent detrimental shifts in lifestyle patterns. This upsurge underscores the intricate interplay between economic prosperity and its unintended consequences on health. (*e.g.*, increased high-fat diets and reduced physical activity)[1]. Drawing upon data from the National Health and Nutrition Examination Survey, it is evident that the prevalence of HUA in the United States has risen, shifting from 18.2% during the period of 1984-1988 to 20.1% in the more recent timeframe of 2015-2016, highlighting a steady increase over the years[2]. HUA can manifest in various clinical presentations, including gout, kidney stones, and cardiovascular diseases (CVDs)[3]. HUA does not always develop into gout, it is associated with increased risk of cardiovascular disease (CVD) (*e.g.*, hypertension[4], heart failure, coronary artery disease[5], atrial fibrillation[6], and acute stroke[7]), as well as acute kidney injury[8], chronic kidney disease[9], and greater decline in renal function.

Currently, the clinically commonly used uric acid (UA)-lowering drugs are mainly divided into two categories: (1) Drugs that inhibit UA production; and (2) Drugs that promote UA excretion. Despite demonstrating therapeutic effectiveness, these medications are often limited in clinical application due to their adverse effects. For example, allopurinol has the potential to trigger a severe and potentially life-threatening hypersensitivity reaction, thereby constraining its widespread utilization[10], benzbromarone may cause hepatotoxicity[11], febuxostat can potentially cause severe rhabdomyolysis and rasburicase is known to trigger rapid hypersensitivity reactions. Given the limitations of current therapeutic drugs for HUA and the myriad of complications associated with it, it has become particularly urgent to find a new, safe, and effective drug to treat HUA.

USING THE GUT MICROBIOME AS A MEDIUM, EXPLORE THE THERAPEUTIC EFFECT OF *POECILOBDELLA MANILLENSIS* LYOPHILIZED *POWDER ON HUA*

Leeches, particularly Hirudo species, hold a historical significance in traditional Chinese medicine, with their earliest mention traced back to the "Shennong Materia Medica", an ancient pharmacopeia from the Eastern Han Dynasty. Among these, *Poecilobdella manillensis*, colloquially known as the Philippine cattle leech or Manila's medical leech, belongs to the esteemed genus of medicinal vermiculite leeches, further expanding the realm of traditional healing practices[12]. This expansive leech species has a broad geographical range, prevalently inhabiting various regions across Southeast Asia, including the Chinese of Guangxi Zhuang Autonomous Region among others.

With the development of modern science and technology, especially the in-depth research on intestinal microbiota and metabolomics[13], we are able to gain a deeper understanding of the scientific mechanisms behind them. Many previous studies have focused on the therapeutic effects of hirudin, but the relevant mechanisms remain unclear, and there have been no experimental reports on leech total protein (LTP) reducing UA. This study explores the potential mechanism of *Poecilobdella manillensis* in the treatment of HUA based on the regulation of intestinal microbiota and host metabolism.

Changes in gut microbiota are closely related to the metabolism of serum UA

Gut microbiota dysbiosis typically leads to imbalances in metabolites such as short-chain fatty acids, trimethylamine, and amino acids[14]. These changes in metabolites may further impact UA metabolism and excretion, exacerbating the symptoms of HUA. Additionally, gut microbiota dysbiosis can impair intestinal barrier function, resulting in the translocation of bacteria or bacterial products like lipopolysaccharide (LPS)[15]. Elevated serum LPS levels can trigger chronic inflammation, thereby increasing the risk of HUA[16].

Poecilobdella manillensis exerts its therapeutic effects on HUA by modulating gut microbiota through a multi-target and multi-pathway mechanism

This investigation unveils the innovative therapeutic promise of *Poecilobdella manillensis* in addressing HUA *via* a dual-pronged mechanism, offering a fresh perspective on its therapeutic applications: (1) Directly regulating UA levels; and (2) Restoring kidney and intestinal barriers. The research underscores the role of proteins in *Poecilobdella manillensis* in correcting gut microbiota dysbiosis and modulating crucial metabolic pathways, particularly those involving sphingolipid and galactose metabolism. Essentially, the findings elucidate the dual functions of LTP (likely referring to a specific protein or active component in *Poecilobdella manillensis*, though LTP is not a commonly recognized acronym for this context), which reduces UA synthesis by inhibiting xanthine oxidase (XOD) activity and promotes UA excretion by regulating different UA transporters in the kidney and intestine[17]. By decreasing UA salt synthesis and enhancing renal UA salt excretion, researchers ultimately demonstrate the remarkable therapeutic potential of LTP in lowering UA levels. This is the first study to uncover that LTP can ameliorate HUA progression by reprogramming gut microbiota and metabolic profiles. It should be noted that the clinical use of *Poecilobdella manillensis* has been associated with certain risks. Previous studies have characterized and analyzed the intestinal bacterial and fungal communities of the Asian medicinal leech, *Poecilobdella manillensis*, through sequencing methods. The results indicate that the gut microbiota of leeches may pose a high risk of opportunistic infections[18]. Some individuals may have allergic reactions to the bites or saliva of leeches, which can range from mild to severe, furthermore, The inadequate exploration of their chemical composition hinders the establishment of robust quality standards for animal-derived medications, thereby contributing to a disorganized market landscape[19]. This is a limitation of the clinical use of the drug.

Limitations of the study

While this study provides novel therapeutic avenues for the treatment of HUA and elucidates the mechanism of LTP in regulating gut microbiota to impact HUA, it is not without its limitations. Firstly, concerning clinical research: Limited sample size. Current research on the use of the freeze-dried powder of *Poecilobdella manillensis* for HUA primarily relies on animal experiments, such as mouse or rat models, with relatively small sample sizes[20,21]. This may not adequately reflect the drug's efficacy and safety in humans. Absence of clinical trials: Despite promising results from animal studies indicating a UA-lowering effect, there is a lack of large-scale, double-blind, randomized controlled clinical trials to validate its therapeutic effects and safety in humans. Secondly, the complexity of the mechanism of action: Multi-target effects. The freeze-dried powder of *Poecilobdella manillensis* likely exerts its UA -lowering effects through multiple pathways and targets, including inhibiting XOD activity and modulating UA transporters. However, this multi-target approach adds to the complexity and uncertainty of its pharmacological mechanism, potentially leading to variations in therapeutic outcomes among individuals. While the freeze-dried powder of *Poecilobdella manillensis* holds promise for the treatment of HUA, its limitations cannot be overlooked. Future endeavors should prioritize conducting more extensive, high-quality clinical studies to confirm its efficacy and safety and to explore optimal usage patterns and indications. Furthermore, attention must be given to potential safety concerns and drug interactions to ensure its safe and effective application in clinical settings.

Future directions of Poecilobdella manillensis therapy for HUA encompass technological optimization and interdisciplinary integration

Firstly, we can further leverage modern molecular biology techniques to delve into the specific interactions between the constituents of *Poecilobdella manillensis* freeze-dried powder and genes related to UA metabolism, uncovering the precise molecular mechanisms underlying its UA-lowering effects. Additionally, integrating multi-omics approaches such as transcriptomics and proteomics[22] can provide a comprehensive understanding of the biological effects of *Poecilobdella manillensis* freeze-dried powder in the treatment of HUA. Secondly, large-scale, double-blind, randomized controlled clinical trials should be conducted to validate the efficacy and safety of *Poecilobdella manillensis* freeze-dried powder in human patients with HUA. Furthermore, we should investigate the combination effects of *Poecilobdella manillensis* freeze-dried powder with existing UA-lowering medications, exploring its potential to enhance efficacy and mitigate side effects. Lastly, we can expand its application areas, for instance, in CVD prevention: Given the close correlation between HUA and CVDs[23], future research can delve into the potential of *Poecilobdella manillensis* freeze-dried powder in preventing and treating CVDs. In addition, given the unsafe nature of the clinical use of *Poecilobdella manillensis*, more relevant pharmacological and toxicological studies should be conducted in the future to enhance its safety profile.

CONCLUSION

The treatment of HUA represents an urgent public health challenge and existing therapies still face numerous issues. The gut microbiota, known as the second genome, holds promise for unraveling the mechanisms underlying HUA and other metabolic disorders, potentially leading to combined therapeutic strategies. *Poecilobdella manillensis* freeze-dried powder shows immense potential in the treatment of HUA. Moving forward, it is imperative to intensify both basic research and clinical trials, explore combination therapies, and broaden its application areas to promote its widespread clinical adoption and development.

FOOTNOTES

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Country of origin: China

ORCID number: Kang-Ming Huang 0000-0003-0914-6543; Hong-Bin Chen 0000-0002-8956-6814; Jin-Rong Lin 0009-0001-4712-2553.

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