Biosaintifika 17 (2) (2025): 349-357 p-ISSN 2085-191X | e-ISSN 2338-7610
Journal of Biology & Biology Education https://journal.unnes.ac.id/nju/index.php/biosaintifika

Modulatory Effects of Noni (*Morinda citrifolia*) Fruit Polysaccharide Syrup on IgG Production and T Cell Activity

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Submitted: 2025-03-22. Revised: 2025-05-26. Accepted: 2025-07-30.

Abstract. Noni fruit containing polysaccharides, has the potential to be developed into pharmaceutical products such as SPF syrup. The content of noni fruit polysaccharides is known to increase the proliferation of T lymphocyte cells, the regulation of the immune system molecularly, especially with regard to antibodies (IgG), $CD4^+$, and $CD8^+$, is still not widely studied. The aim of this study was to assess the impact of SPF syrup on the modulation of immunoglobulin G (IgG) and T lymphocytes. The study was conducted on female Wistar rats aged 8-9 months, which were given SPF syrup orally at doses of 25, 50, and 100 mg/kgBB for 31 days. Mice were vaccinated against hepatitis B every week. Blood samples were taken on day 31 to measure IgG levels by the ELISA method and T cells ($CD4^+$ and $CD8^+$) by flow cytometry. The results showed that SPF administration had a significant effect on IgG levels ($p<0.05$), and there were no significant changes in T lymphocyte cells ($CD4^+$, $CD8^+$) ($p>0.05$). Histopathological examination showed that long-term induction of hepatitis B caused damage to the liver and kidney, but SPF did not affect the condition of these organs. SPF that contains polysaccharides can be an innovative component in immunostimulant formulations.

Keywords: CD4+; CD8+; IgG; Immunomodulator; Noni fruit; Polysaccharide

How to Cite: Anwar, L. O. M., Sasmito, E., Rasydy, L. O. A., Ismoyowati, T. W., Hashim, S. M. R., Siregar, R., Hutagaol, E. K., Bratajaya, C. N. A., Sartika, A., Sanjaya, D., Rohmah, H. N. F., & Ximenes, J. M. C. (2025). Modulatory Effects of Noni (*Morinda citrifolia* L.) Fruit Polysaccharide Syrup on IgG Production and T Cell Activity. *Biosaintifika: Journal of Biology & Biology Education, 17(2)*, 349-357.

DOI: http://dx.doi.org/10.15294/biosaintifika.v17i2.26258

INTRODUCTION

Defends the body against different diseases, including those caused by foreign microorganisms. The immune system is designed to be a biological defense mechanism that protects an individual's body from a plethora of diseases. The immune system also serves a lot of functions, like maintaining a person's health (J. E. Almeida et al., 2025; Arifka et al., 2024; Justiz Vaillant et al., 2025). Each organ in the body relies on specific types of cells and molecules to manage its local innate immune responses (Drummond & Lionakis, 2019; Ng et al., 2023). When these immune responses are compromised, the body becomes more vulnerable to infections caused by viruses or bacteria. This not only heightens the risk of disease development but also weakens the body's ability to fight off infections effectively (Al-Worafi, 2023; Morales et al., 2023; Theodorakis et al., 2024; Wrona et al., 2024).

Natural compounds are seen as some of the most promising and effective options for strengthening immune responses (Guo et al., 2024). Noni fruit in particular is very high among natural remedies, highly regarded by Polynesians as a mainstay remedy. For centuries, it has been used as an alternative to treat inflammation, abscesses, angina, diabetes, ranula, abdominal fibromas, as well as scorpionfish sarcoptes corticis, and it is still intact as an ancient medicine both in folk medicine circulation today(Anand et al., 2019; Anwar et al., 2024; Hooda et al., 2024; Singh et al., 2024; W. Sun & Shahrajabian, 2023;

West et al., 2018). Noni plant (*Morinda citrifolia*) is used across the world as a remedy for more than forty kinds of diseases (É. S. Almeida et al., 2019; Obeng-Boateng et al., 2024; Ponmurugan et al., 2025). The crude extracts from different parts including the fruit of the plant have been described to contain a plethora of bioactive substances a.o. amino acids, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, sugars and terpenoids, etc along with indispensable trace elements (Chebabe et al., 2025; Trivadila et al., 2025; B. Zhang et al., 2025). These constituents give the plant its multi-faceted therapeutic potential, furthering its traditional and modern medicinal applications (Liu et al., 2024). Research by Hou et al. (2025) suggests that the noni fruit polysaccharides have considerable immunomodulatory properties. Polysaccharides are considered to be non-toxic and side effect free natural products (F. Zhang et al., 2017). Sasmito et al., (2017) has a single standardized polysaccharide fraction (SPF) of noni fruit in syrup form, glucose being the normalization marker at a concentration of ~5%. Standardization is necessary in order for each batch to have the same weight and efficacy so that the product efficacy can be reliably assessed with respect to its therapeutic effects. Therefore, investigating the role of SPF syrup for the immune system is necessary to confirm its immunomodulatory advantages. In combination with other potential substrates for example IL-2 and IFN-γ SPF has been assessed. IL-2 levels decreased while there was an increase in IFN-γ (Yudhawan et al., 2020).

Natural markers of immune function in diverse experimental models may be observationally derived from immune responses as described for several immune parameters (e.g., antibody (IgG); and a measure of the ratio of the $CD4^+$ and $CD8^+$ T cell marker molecule). Antibodies function as an opsonin for cellular immunity: IgG is important for antigen destruction and it also has a half-life of ~three weeks following production as opposed to the other antibodies like IgA and IgM that are brought only transiently, in nature. $CD4^+$ T cells subset differentiate into Th1/Tdth with the primary function of attracting macrophages and other immune cells to the site and participating in inflammatory responses during sensitization. $CD8^+$ T cells are needed to eradicate cells infected with the virus which also offers a part of the immune system defense (Ahrends et al., 2017; Alam et al., 2025; Hernández et al., 2025; Lees, 2020; Thakur & Gaspar, 2023).

The liver and kidneys, among other organs, are vital in supporting the body's ability to produce antibodies and T cells (Hu et al., 2016; Rabb, 2002; Yang et al., 2024). The liver is the origin of about 23% of T cells and 5% of B cells. In order to protect against infections, the B cells continue to proliferate and produce immunoglobulins (Ibidapo-Obe & Bruns, 2023; Y. Wang & Zhang, 2019). However, the kidneys ensure a balanced relationship between tissue damage and regeneration by keeping innate immune cells, such as dendritic cells, macrophages, NK cells, and some innate lymphocytes, in a state of homeostasis (Marianti et al., 2024; Mu et al., 2025; M. Wang et al., 2024; R. Wang et al., 2021, 2021). Injury to these organs can disrupt immune system regulation, making it more difficult for the body to fight infection and maintain a balanced immune system. Therefore, the aim of this study was to assess the immune response elicited by SPF syrup, with particular attention to IgG levels and the ratio of T cell marker molecules ($CD4^+$ and $CD8^+$). The study also looked at how SPF administration affects kidney and liver health, providing information on its possible efficacy and safety. Ultimately, the results of this study may help SPF become a more effective treatment for immune regulation and organ health in the future.

METHODS

Animal Preparation

The test subjects used in this study were 8-9-week-old female SD galus rats, sourced from the Faculty of Pharmacy at Gadjah Mada University. The animals were grouped and housed in research cages, where they were kept under standard laboratory conditions, with a temperature maintained at 27 ± 2ºC and a 12-hour light-dark cycle. Animals have received ethical approval with number 00085/04/LPPT/VIII/2018 by Gadjah Mada University.

Sample Preparation

The test sample, in the form of SPF syrup, was obtained directly from the research conducted by Sasmito et al. (2017), which included the determination of marker levels, organoleptic tests, and stability testing of the preparation.

Animal Grouping

A total of 30 test animals were used in this study, divided into 6 groups, with 5 rats per group. Group K1 served as the negative control, while Groups K2-K6 were designated as treatment

groups. K1 rats did not receive the hepatitis B vaccine or SPF syrup; they were only administered the SPF solvent (without polysaccharides). K2 received the hepatitis B vaccine and SPF solvent. K3 received the hepatitis B vaccine and SPF syrup at a conversion dose of 25 mg/kg body weight. K4 was administered the hepatitis B vaccine and SPF syrup at a conversion dose of 50 mg/kg body weight. K5 received the hepatitis B vaccine and SPF syrup at a conversion dose of 100 mg/kg body weight. Finally, K6 was given only SPF syrup at a conversion dose of 100 mg/kg body weight, without the hepatitis B vaccine or SPF solvent.

ELISA Assay Test

On day 31, blood samples were collected from the eyelid using a heparinized capillary through the retroorbital plexus. The collected blood was placed in containers containing EDTA to prevent clotting, while being gently shaken. A total volume of approximately 2-3 mL of blood was drawn. The samples were incubated at 37°C before being centrifuged at 3000 rpm for 10 minutes. The resulting plasma was then used to measure IgG levels using the ELISA assay method. The optical density (OD) values were recorded and calculated using an ELISA reader.

Flow Cytometry Test

On day 31, blood samples were collected from the eyelids using a heparinized capillary. The blood was placed in containers containing EDTA and gently shaken to prevent clotting. A total volume of approximately 1-1.5 mL of whole blood was collected. The samples were stored at -4°C with a maximum storage duration of 72 hours. $CD4^+$ and $CD8^+$ levels were subsequently analyzed using flow cytometry.

Liver and Kidney Histology

Within a maximum of 7 hours post-blood collection, the rats' organs (liver and kidneys) were harvested and immediately preserved in 10% formalin. The liver and kidney tissues were sliced as thinly as possible, with both longitudinal and transverse incisions made. Hematoxylin-eosin staining was applied to the liver and kidney preparations, followed by an evaluation of the anatomical pathology in the liver and kidney tissues.

Data Analysis

Each data was analyzed using a one-way ANOVA test through the GraphPad Prism application. If significance was found, the analysis was followed by Tukey's test to compare across groups

RESULTS AND DISCUSSION

The current study explores the effect of the SPF syrup obtained from the noni (*Morinda citrifolia*) fruit on the immune system at the molecular level. The noni fruit is rich in bioactive compounds, particularly polysaccharides with possible immunomodulatory properties. According to Abbas (2017), the function of polysaccharides as self-sufficient antigens is that they bind to B cell receptors and subsequently stimulate the activation of $CD4^+$ (T -helper) and $CD8^+$ (cytotoxic T) lymphocytes. Such interactions are often characterized by low binding affinity and primarily IgM antibodies are produced as a response.

The effects of SPF syrup from noni fruit were evaluated in a rat model, which was divided into six experimental groups. K1 served as the negative control, receiving syrup devoid of the polysaccharide fraction. K2 was administered only the hepatitis B vaccine once a week, without SPF syrup, to serve as a baseline for antibody induction. K3 to K5 were treated with varying doses of SPF syrup (25, 50, and 100 mg/kg body weight), along with the weekly hepatitis B vaccine for a duration of three weeks. K4 was administered SPF syrup at a dose of 100 mg/kg body weight without the hepatitis B vaccine. The total treatment duration was 31 days, including a 7-day acclimatization period. Blood samples were collected via retroorbital plexus for subsequent analysis of total IgG levels and T lymphocyte populations ($CD4^+$ and $CD8^+$) using ELISA and flow cytometry.

Table 1. Results of the analysis of antibody levels (IgG) in each group

Group	IgG (ng/mL)
K1 (negative control)	99.54 ±36.90
K2 (vaccine only)	79.07 ±14.75
K3 (SPF 25 mg dose + vaccine)	167.94 ±2.15
K4 (SPF 50 mg dose + vaccine)	82.80±13.07
K5 (SPF 100 mg dose + vaccine)	125.50± 42.79
K6 (SPF 100 mg dose only)	69.27±17.29

$p<0,05$; significant

Among the test groups, the highest IgG levels were observed in K3. This suggests that the administration of SPF syrup from noni fruit

significantly enhances IgG production ($p<0.05$). The observed response is consistent with the characteristics of polysaccharides, which function as independent antigens and primarily induce the production of IgM. IgM is the earliest antibody produced post-antigen exposure, typically within 3-4 days, followed by IgG production (Rijkers & Meek, 2019; Sathe & Cusick, 2022; Sundling et al., 2021). A low dose (25 mg) may optimally activate the immune system, thereby increasing IgG antibody production. This is in line with the concept that low doses of an immunostimulating agent may trigger a more effective immune response than higher doses, which may result in tolerance or immunosuppression. This is in line with research conducted by Lajqi et al (2023) who stated that exposure to low doses of an immune stimulus, can induce an enhanced immune response through activation of the mTOR pathway, while exposure to high doses tends to induce immune tolerance through activation of the AMPK pathway. This phenomenon suggests the existence of a multiple-dose response (hormesis) in the immune system, where low doses stimulate and high doses suppress immune responses.

Similarly, the analysis of $CD4^+$ and $CD8^+$ lymphocyte populations revealed no significant differences ($p > 0.05$) between the groups. The highest $CD4^+$ count was observed in K1, while the highest $CD8^+$ count was found in K4. These findings indicate that polysaccharides, as standalone antigens, exert minimal impact on T lymphocyte proliferation. This aligns with the established paradigm that T-cell activation an essential prerequisite for eliciting an antibody response is predominantly required for the immunogenicity of T-cell-dependent antigens. Therefore, polysaccharides, which act as independent antigens, do not significantly alter the number of $CD4^+$ and $CD8^+$ T cells.

Histological examination of the liver and kidneys revealed significant findings. In K2 and K5, fatty degeneration of the liver was observed, characterized by the presence of vacuoles of varying sizes with well-defined borders in the cytoplasm. In contrast, K3 exhibited tubular necrosis in the kidneys. These results indicate that repeated administration of the hepatitis B vaccine over three weeks can lead to organ damage, particularly in liver cells. The hepatoprotective effects of SPF syrup cannot be conclusively determined in this study, as further investigations are required, including the assessment of SGPT and SGOT levels. This is very interesting information about the side effects of the Hep B vaccine.

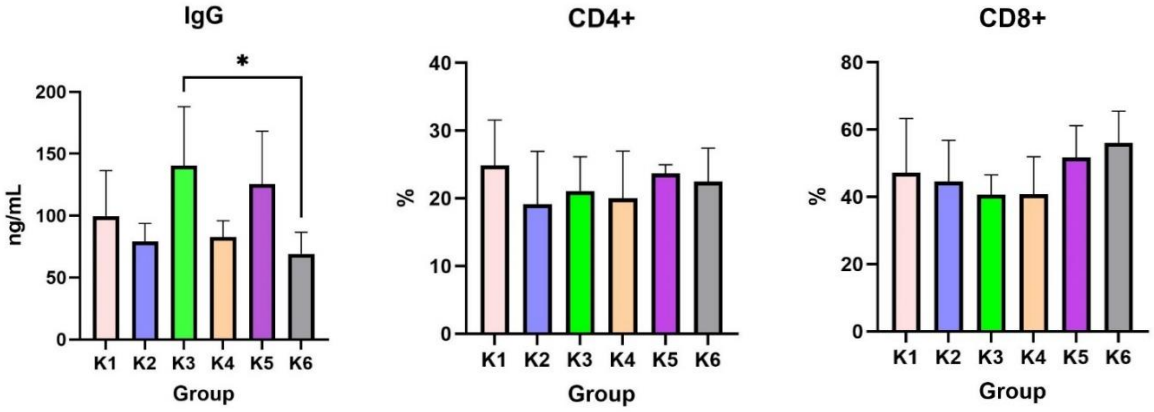

Figure 1. Diagram of IgG values and lymphocyte cells ($CD4^+$ and $CD8^+$ cells). There was a significant difference in IgG values ($p<0.05$) while there was no significant difference in lymphocyte cells ($p>0.05$).

Table 2. Results of analysis of T cells ($CD4^+$ and $CD8^+$) in each group

Group	CD4+ (%)	CD8+ (%)
K1 (negative control)	24.87±6.67	47.24±16.05
K2 (vaccine only)	15.87±2.93	40.00±7.74
K3 (SPF 25 mg dose + vaccine)	21.12±5.02	40.67±5.90
K4 (SPF 50 mg dose + vaccine)	17.25±3.69	45.41±5.08
K5 (SPF 100 mg dose + vaccine)	23.69±1.28	51.75± 9.41
K6 (SPF 100 mg dose only)	22.49±4.91	52.35±5.57

$p> 0.05$; not significant

Table 3. Results of histopathological analysis of the liver and kidneys by staining with hematoxylin and eosin

Group	Liver	Kidney
K1	NPC	NPC
K2	Periportal and medzonal fatty degeneration	NPC
K3	NPC	Tubular necrosis is accompanied by lymphocyte infiltration
K4	NPC	NPC
K5	Degeneration fats (mikrovakuoler)	NPC
K6	NPC	NPC

*NPC: no pathological changes
*Fatty degranulation is characterized by vacuoles of various sizes with clear boundaries in the cytoplasm

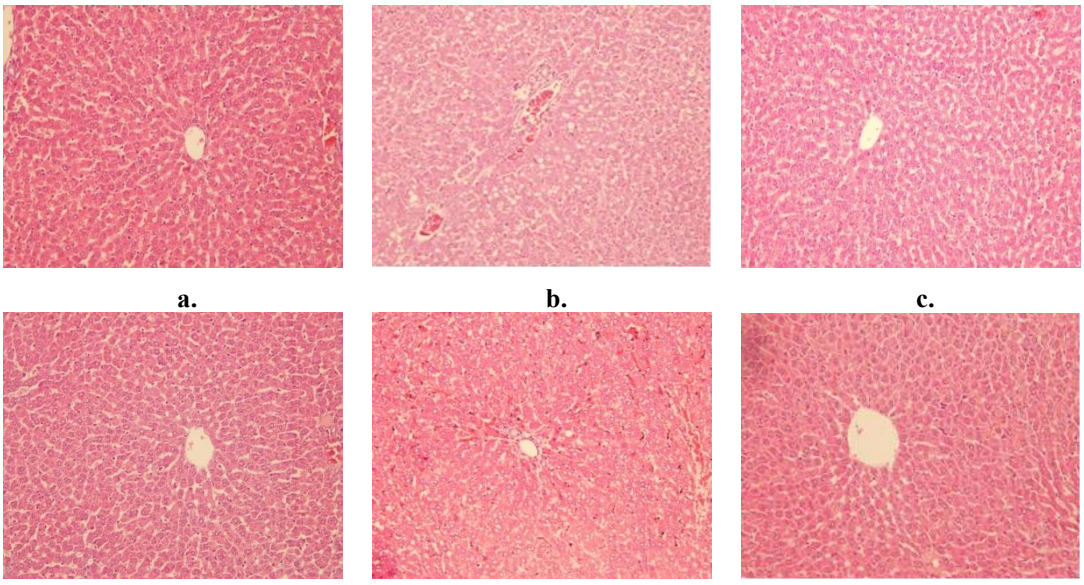

Figure 4. Liver organs after treatment in each test group (a) K1 (b) K2 (c) K3 (d) K4 (e) K5 and (f) K6. There is no change in the pathophysiology of organs for group K1, K3, K4 and K6. In groups K2 and K5 there was degenerative degeneration that occurred in the periportal and medzonal and microvacuoles.

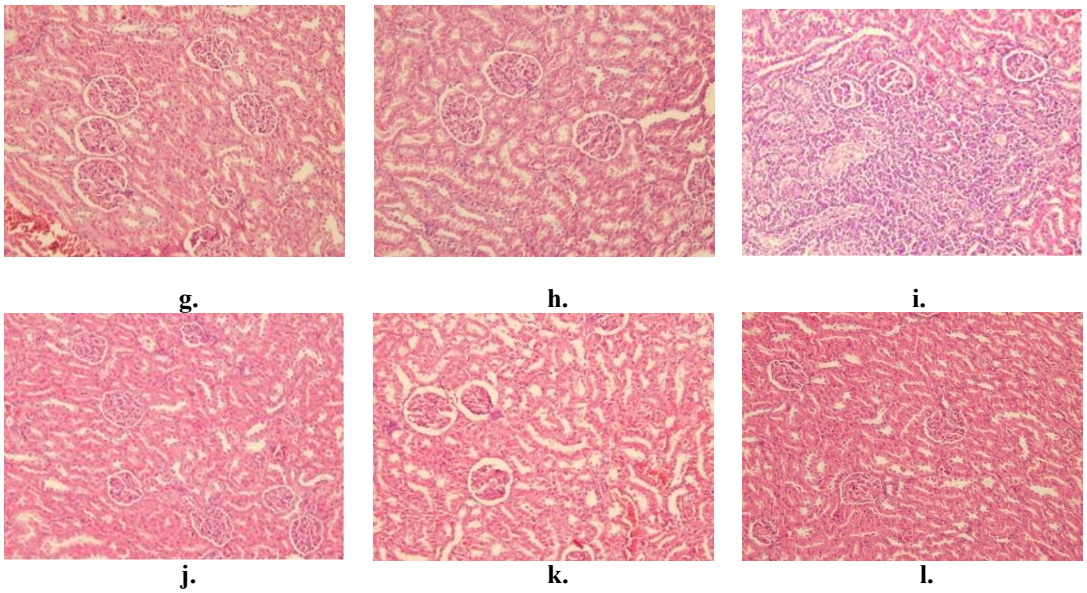

Figure 5. Kidney organs after treatment in each test group : (g) K1 (h) K2 (i) K3 (j) K4 (k) K5 and (l) K6. The K1, K2, K4, K5, and K6 groups did not experience pathophysiological changes in organs. K3 group had necrosis in the tubular section

In general, this study suggests that polysaccharides are independent antigenic compounds that do not significantly influence the formation of specific antibodies such as IgG or T cell responses ($CD4^+$ and $CD8^+$). The immune response to polysaccharides predominantly involves IgM production, but further research is necessary to substantiate this hypothesis. Pure polysaccharides are generally considered to be T-independent antigens due to their limitations in being processed and presented through the MHC class II pathway, which is required for $CD4^+$ and $CD8^+$ T cell activation. This leads to limited immune responses to pure polysaccharide antigens. Nonetheless, most non-zwitterionic polysaccharides remain incapable of being presented through MHC class II efficiently, thus not inducing significant T cell activation. This explains why administration of purified polysaccharides often does not result in significant increases in $CD4^+$ and $CD8^+$ cell populations (Cobb et al., 2004; L. Sun et al., 2016; Undale et al., 2004). Additionally, this study highlights that prolonged administration of the hepatitis B vaccine can lead to organ damage, particularly affecting liver cells, emphasizing the need for further exploration of vaccine-induced side effects. Hepatitis B vaccine contains adjuvants such as aluminum hydroxide, such adjuvants may contribute to liver damage, especially at low doses where detoxification systems may be less activated. Aluminum as an adjuvant is known to trigger oxidative stress and inflammation in liver tissue (Hamza et al., 2012). At low doses tubular necrosis also occurs. Low doses of the SPF may act as a potent immunostimulant, triggering T cell activation and IgG antibody production. However, this excessive immune activation may cause infiltration of immune cells, such as lymphocytes, into the kidney tissue, leading to inflammation and tubular necrosis (Lim et al., 2024; Miguel et al., 2011). Notably, this study provides information that SPF can be developed as an immunostimulant.

CONCLUSION

Administration of SPF syrup produced significant effects on the production of IgG. Meanwhile, T cell markers ($CD4^+$ and $CD8^+$) did not undergo significant changes. This could be attributed to the polysaccharide content, which acts as an independent antigen. Polysaccharides mainly affect the production of specific antibodies without affecting T cell marker molecules, such as $CD4^+$ and $CD8^+$. However, it is necessary to conduct long-term studies on chronic toxicity as well as early clinical trials in humans to confirm its safety and therapeutic benefits.

ACKNOWLEDGEMENTS

Thanks to Universitas Medika Suherman and Universitas Gadjah Mada for facilitating this research.

AUTHOR CONTRIBUTION STATEMENT

All authors played essential roles and made substantial contributions to the development and completion of this manuscript. The research funding was secured by La Ode Muhammad Anwar. The investigation phase was collaboratively conducted by La OMA, ES, RS, EKH, CNAB, DS, and HNFR. The methodological framework was developed by La OMA, ES, La OAR, TWI, SHRH, and AS. Project administration was overseen by La OMA, ES, and La OARES and JMCX was responsible for validating the study. All contributors reviewed and approved the final version of the manuscript and collectively accept full responsibility for the integrity and accuracy of the work.

INFORMED CONSENT STATEMENT

Informed consent from all subjects involved in the study was obtained. Each subject group was given a detailed explanation of the purpose, procedures, potential risks, and benefits of the study. This study has obtained ethical approval from the authorized institution, Gajah Mada University.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this paper.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

There are no artificial intelligence (AI) tools used in the creation, analysis or writing of this manuscript. All aspects of the research, including data collection, interpretation, and manuscript preparation, were conducted entirely by the authors without the assistance of AI-based technology.

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