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Black Garlic Supplementation and Glomerular Protection in Hyperuricemic Rats: A Study on Kidney Health Prevention

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ABSTRACT

Introduction: Hyperuricemia is a significant risk factor for the development of chronic kidney disease. Excessive uric acid can deposit in the kidneys, triggering inflammatory reactions and oxidative stress, leading to structural damage in the glomeruli. Black garlic, with its antioxidant and bioactive compounds, has the potential to protect the kidneys from hyperuricemia-induced damage. Our objective is to evaluate the effect of black garlic supplementation on the histopathological features of glomeruli in a hyperuricemic rat model.

Methods: This study was an analytical observational study using Biological Remnant Materials (BRM) from a previous study. The sample consisted of 30 male Sprague-Dawley rats divided into 5 groups: disease control, drug control (allopurinol), and 3 black garlic dose groups (240 mg/day, 480 mg/day, and 960 mg/day). Data were collected through histopathological examination of kidney tissue using the glomerular damage scoring method (0-3). Data analysis was performed using one-way ANOVA and post hoc LSD tests.

Results: Black garlic demonstrated protective effects on the histopathological features of glomeruli in hyperuricemic rats. The 240 mg/day dose showed the most significant improvement in kidney health, reducing glomerular damage scores compared to the disease control group ($p < 0.05$). These findings suggest that black garlic can serve as a preventive agent against kidney complications caused by hyperuricemia.

Conclusion: Black garlic provides protective effects on glomerular histopathology in hyperuricemic rats, with the 240 mg/day dose being the most effective. These results suggest potential use for black garlic in preventing kidney complications in hyperuricemia.

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INTRODUCTION

Chronic kidney disease (CKD) is a growing global health burden, with hyperuricemia being a significant but underexplored risk factor (1). Hyperuricemia has been identified as an important risk factor for the development of CKD, as excess uric acid accumulated in the kidneys can trigger inflammatory reactions and oxidative stress, ultimately leading to damage of renal structures (2). Although studies have shown an association between hyperuricemia and increased risk of CKD, the molecular mechanisms underlying this association are still not fully understood. Currently, the treatment of hyperuricemia often relies on drugs such as allopurinol and febuxostat (3), but their limited efficacy and potential toxicity, especially in patients with impaired renal function, raise the need to find safer alternative therapies. This is where black garlic, known to be rich in antioxidant compounds such as S-

allyl-cysteine (SAC) (4), emerges as a promising candidate. Several early studies have shown that black garlic has anti-inflammatory and antioxidant properties that may protect the kidneys from damage caused by hyperuricemia (5). However, these studies are still limited and do not provide a comprehensive understanding of the protective mechanisms of black garlic in the context of hyperuricemia-induced kidney damage.

Black garlic, a natural antioxidant, offers a promising alternative for preventing kidney damage. This study aims to address the gap in knowledge by evaluating black garlic's protective effects on kidney health. The burden of CKD is increasing, causing a heavy healthcare burden and high treatment costs for national healthcare systems (6). According to the latest data from the World Health Organization (WHO), it is estimated that more than 10% of the global population suffers from CKD (7). This figure is even higher in low- and middle-income countries, which often have limited access to adequate healthcare. Therefore, the WHO has identified CKD as a top priority in efforts to improve global health (8,9).

Hyperuricemia, or elevated blood uric acid levels, is an important risk factor in the development of chronic kidney disease (10). Excessive uric acid can accumulate in the kidneys, causing tissue damage through inflammatory and oxidative stress mechanisms (11). Uric acid crystals that accumulate in kidney tissues trigger activation of the immune system, which eventually leads to injury in the glomeruli and renal tubules (12). Additionally, hyperuricemia is known to activate the renin-angiotensin system (RAS), which increases glomerular blood pressure and exacerbates kidney injury (2). Recent studies have shown that lowering uric acid levels through therapies like allopurinol can slow the progression of CKD in patients with hyperuricemia, though the use of allopurinol in patients with kidney impairment requires careful monitoring due to its potential toxicity (13).

Despite numerous studies to understand the risk factors and pathogenesis of CKD, there are still important knowledge gaps that need further exploration. One aspect that remains poorly understood is the role of hyperuricemia, or high blood uric acid levels, in kidney damage (14). Several studies have shown a relationship between hyperuricemia and increased risk of CKD, but the underlying molecular mechanisms are still unclear (15). This study aims to address these knowledge gaps by investigating the impact of hyperuricemia on the histopathological structure and function of the kidneys in a rat animal model (16). The study also explores the potential of black garlic as an alternative therapy to reduce kidney damage caused by hyperuricemia (17).

Black garlic, as a natural ingredient rich in bioactive compounds, has attracted attention in health research due to its potential in addressing various diseases, including kidney disease. Several studies have shown that black garlic supplementation may have protective effects on the kidneys through various mechanisms, including anti-inflammatory, antioxidant properties, and reducing uric acid levels in the body (18).

Hyperuricemia is also often associated with kidney disease through an increased risk of hypertension and metabolic syndrome, both of which further deteriorate kidney function (12). Several studies have shown that controlling uric acid levels not only reduces the risk of CKD progression but can also improve overall kidney function in patients with early-stage kidney disease (11,19). Additionally, recent research has begun to explore the use of natural agents, such as black garlic extract, which possesses antioxidant and anti-inflammatory properties, in efforts to prevent kidney damage related to hyperuricemia (20). Although pharmacological therapies like allopurinol and febuxostat remain the standard for managing hyperuricemia, the development of preventive strategies based on diet and natural agents shows potential to expand treatment options for patients at high risk for kidney disease (21).

Building on these findings, black garlic offers promising potential as a natural therapeutic agent. Its rich composition of antioxidants, including S-allyl-cysteine (SAC), has been shown to protect against oxidative stress and inflammation, both of which play critical roles in the progression of kidney damage in hyperuricemia (5). Furthermore, black garlic has demonstrated the ability to regulate important enzymes involved in purine metabolism, contributing to a reduction in uric acid levels. This makes black garlic an attractive candidate for mitigating the adverse effects of hyperuricemia on renal function, particularly in preventing the progression to chronic kidney disease (22). However, more in-depth studies are needed to elucidate the precise mechanisms by which black garlic exerts its renal protective effects, especially at the cellular and molecular levels.

Histopathological damage to the glomerulus can significantly impair kidney function, as the glomerulus is essential for blood filtration (23). Damage can lead to reduced filtration, causing toxins and waste to accumulate in

the body. A common consequence is proteinuria, where protein leaks into the urine due to damaged glomerular membranes, potentially leading to hypoalbuminemia and edema (24). Chronic glomerular damage can progress to chronic kidney disease (CKD), increasing the risk of end-stage renal disease (ESRD), which may require dialysis or a kidney transplant. Additionally, damaged glomeruli can activate the renin-angiotensin-aldosterone system (RAAS), resulting in high blood pressure, further worsening kidney function (25). Fluid retention and edema are also common, as the kidneys fail to remove excess fluid. In severe cases, uremia can occur, where nitrogenous waste products build up in the blood, leading to symptoms like nausea, fatigue, and confusion.

Given the potential benefits of black garlic, this study aims to provide a comprehensive analysis of its effect on kidney health in the context of hyperuricemia. By focusing on histopathological changes in the glomeruli, a key functional unit in the kidney, the research seeks to determine whether black garlic supplementation can prevent or reduce kidney damage caused by high uric acid levels. The findings from this research could contribute valuable insights into the development of new dietary or therapeutic interventions for hyperuricemia-induced kidney complications. Furthermore, by utilizing an animal model, the study seeks to bridge existing knowledge gaps in the role of hyperuricemia in CKD pathogenesis and explore black garlic as a potential preventive strategy for global kidney health. While previous studies have explored the antioxidant effects of black garlic, this research specifically investigates its protective effects on kidney glomeruli in a hyperuricemic model, filling a critical gap in understanding its role in kidney health. This study is unique in its focus on the specific histopathological features of the glomeruli in response to black garlic supplementation, an area that has been relatively underexplored in previous research on dietary interventions for kidney health.

However, further research is needed to gain a deeper understanding of how black garlic may affect the histopathological appearance of glomeruli in hyperuricemia conditions. Thus, this research is expected to provide valuable insights for the development of more effective prevention and treatment strategies for kidney disease globally.

METHOD

This is an analytical observational study using rat kidney organs. This design was chosen to observe and analyze the histopathological features of rat kidney glomeruli in evaluating the protective effect of black garlic on hyperuricemic conditions. The study population consisted of 30 samples of male Sprague-Dawley rats. The rats were divided into five treatment groups: hyperuricemic control, allopurinol drug control, and three black garlic dose groups (240 mg/day, 480 mg/day, and 960 mg/day). The sample size was determined based on the Federer formula calculation. The doses of 240 mg, 480 mg, and 960 mg were selected based on previous studies that demonstrated the efficacy of black garlic in similar animal models, with 240 mg showing the most pronounced effects in earlier experiments on antioxidant activity (26). Doses were selected based on previous studies showing antioxidant efficacy at low levels. Post-hoc LSD was used to compare mean differences between groups to detect subtle but statistically significant changes across treatments.

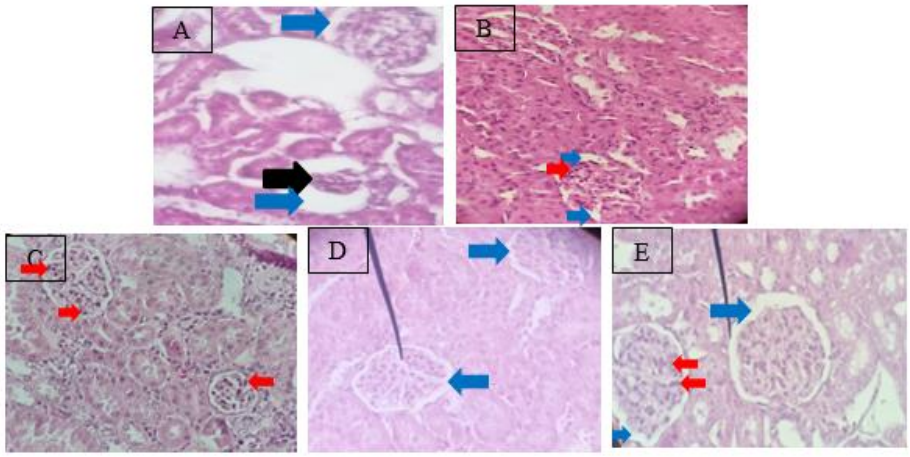
The research was conducted at the animal laboratory of the Faculty of Medicine, Jenderal Soedirman University, Purwokerto, for animal treatment, and at the Pathology Anatomy Laboratory of Prof. Dr. Margono Soekarjo Hospital, Purwokerto, for the preparation and examination of histological slides. This study obtained ethical approval from the Medical Research Ethics Committee (KEPK) of the Faculty of Medicine, Jenderal Soedirman University, with a letter number 001/KEPK/PE/I/2024.

Data were collected through histopathological examination of rat kidney tissue slides. The assessment was performed using the glomerular damage scoring method. Histopathological scoring was performed by evaluating five fields of view per slide at 100x and 400x magnifications. The scores ranged from 0 (no damage) to 3 (severe damage), based on the extent of glomerular changes. The glomerular damage assessment method involves histopathological scoring, where kidney tissue is stained using hematoxylin-eosin (H&E) or other special stains and examined under a microscope at 100x or 400x magnification. Glomerular damage is scored on a numerical scale (0-3), with 0 indicating no damage and 3 indicating severe damage such as fibrosis or necrosis (27). The score is calculated based on several fields of view (typically 5-10) to obtain an average. Multiple researchers may independently assess the samples to ensure consistency (inter-rater reliability). The dependent variable was the

histopathological appearance of the glomeruli, assessed by the glomerular damage score. The independent variable was the administration of black garlic at different doses (240 mg/day, 480 mg/day, and 960 mg/day). Univariate analysis was used to describe each variable. Normality (Saphiro Wilks) and homogeneity (Levene's test) tests were performed to determine the appropriate statistical test. Bivariate analysis using one-way ANOVA was employed to test the hypothesis, followed by a post hoc LSD test if the result was significant. The analysis was performed using SPSS software. Histopathological observations were carried out by researchers under the supervision of a histopathologist to ensure data quality.

RESULTS

In this study, five groups with respective treatments were observed for histopathological outcomes, as shown in Figure 1. That figure 1 illustrates the extent of glomerular damage across treatment groups, with clear signs of protection in the black garlic-treated groups. Specifically, Group C (240 mg/day) shows significantly less cellular damage and reduced inflammatory cell infiltration compared to the hyperuricemic control group. Additionally, in Group D (480 mg/day) and Group E (960 mg/day), a protective effect was also observed, though the extent of improvement was less pronounced than in Group C. This suggests that while higher doses of black garlic continued to provide some level of protection, they did not offer incremental benefits beyond the 240 mg/day dose. In fact, the diminished protective effects at higher doses may indicate a threshold beyond which the efficacy plateaus or even decreases, possibly due to the toxic nature of excessive organosulfur compounds present in black garlic. This dose-dependent trend aligns with findings from other studies that observed similar outcomes, where moderate doses of antioxidants proved to be more effective than higher ones in preventing tissue damage. Based on Figure 1, the group receiving the 240 mg/day dose (Group C) showed the least cellular damage and significantly reduced inflammatory cell infiltration compared to the control group. This dose provided the most significant protection against glomerular damage caused by hyperuricemia.



Notes: Group A (Hyperuricemic Disease Control); Group B (Standard Allopurinol Drug Control); Group C (Black Garlic Treatment 240mg/day dose); Group D (Black Garlic Treatment 480mg/day dose); Group E (Black Garlic Treatment 960mg/day dose).
The red arrow indicates inflammatory cell infiltration; The blue arrow indicates bowman's space edema; The black arrow indicates glomerular cell or tissue death.

Figure 1. Microscopic Appearance of Rat Kidney Glomerulus. H&E Stain. 400x Magnification

The results showed a clear dose-response relationship, with the 240 mg/day group showing the most significant improvement. Groups treated with higher doses (480 mg/day and 960 mg/day) exhibited diminishing returns, possibly due to excessive antioxidant intake, as suggested by previous research. Building on these findings, the effectiveness of the 240 mg/day dose suggests an optimal balance between therapeutic benefit and safety. Higher

doses, such as 480 mg/day and 960 mg/day, may overwhelm the cellular antioxidant defense mechanisms, leading to a pro-oxidant effect. This phenomenon, often referred to as the antioxidant paradox, occurs when excessive antioxidants disrupt redox homeostasis, potentially causing oxidative stress rather than preventing it. Previous studies have shown that while low to moderate levels of antioxidants protect cells from damage, excessive doses can have the opposite effect, contributing to cellular dysfunction and even accelerating tissue injury. This highlights the importance of determining the correct dosage for maximizing the protective effects of black garlic without triggering adverse outcomes. The results of the univariate analysis were obtained by calculating the median, maximum, minimum, mean, and standard deviation of the glomerular damage scores, which are presented in Table 1.

Tabel 1. Results of Univariate Analysis

Kel.	N	Median	Max.	Min.	Rerata	Standar Deviasi
A	6	2,4	2,6	2,2	2,36	±0,1506
B	6	2,0	2,2	1,8	2,00	±0,1789
C	6	1,2	1,4	1,0	1,20	±0,1265
D	6	1,3	1,6	1,2	1,33	±0,1633
E	6	1,5	2,0	1,2	1,56	±0,2944

Notes: Group A (Hyperuricemic Disease Control); Group B (Standard Allopurinol Drug Control); Group C (Black Garlic Treatment 240mg/day dose); Group D (Black Garlic Treatment 480mg/day dose); Group E (Black Garlic Treatment 960mg/day dose).

Based on the bivariate analysis, the results of the Saphiro-Wilk test and Levene's test showed that the data were normally distributed and homogeneous, as the Sig value was >0.05. In the one-way ANOVA hypothesis test, the significance value obtained was 0.000 (sig. <0.05). These results indicate that black garlic had an effect on protecting against glomerular damage in the hyperuricemic white rat model. Furthermore, the results of the post hoc LSD test are presented in Table 2. The selected doses of 240 mg, 480 mg, and 960 mg/day were based on prior evidence suggesting efficacy at low doses in reducing oxidative stress and inflammation. Post-hoc LSD was used to compare mean differences between groups to detect subtle but statistically significant changes across treatments. Based on the table 2, it is known that there is no significant difference (Sig.>0.05) between group C and group D. Almost all comparisons between treatments show significant differences ($p < 0.05$), except between Treatment C and D ($p = 0.240$). Treatment C and D do not have a significant difference, which means these two treatments provide relatively similar effects. Treatment A has highly significant differences ($p = 0.000$) with C, D, and E, indicating that the effect of Treatment A is very different from these three treatments. Treatment B also shows highly significant differences with C and D ($p = 0.000$). The smallest difference (though still significant) exists between Treatment D and E ($p = 0.045$). Overall, this data indicates that most treatments provide statistically different effects, with the exception of the C-D pair which provides similar effects.

Table 2. Results of Post-Hoc LSD Test

Treatment Group		**Sig. value**
A	B	.003
	C	.000
	D	.000
	E	.000
B	A	.003
	C	.000
	D	.000
	E	.001
C	A	.000
	B	.000
	D	.240
	E	.003
D	A	.000
	B	.000

	C	.240
	E	.045
E	A	.000
	B	.001
	C	.003
	D	.045

DISCUSSION

The results of this study showed that administration of black garlic solution had a good effect as protection against glomerular kidney damage in rats induced with hyperuricemia. The active compounds in black garlic such as flavonoids, polyphenols, 5-HMF and SAC are compounds that have antioxidant and anti-hyperuricemic activities so that they can prevent glomerular kidney damage in rats due to hyperuricemia induction (28).

Induction of hyperuricemia can trigger glomerular damage through activation of the immune system due to the presence of uric acid. The immune system activity that occurs can affect the characteristics of kidney cells such as tubular epithelial cells, endothelial cells, and vascular smooth muscle cells in a pro-inflammatory condition. This condition can trigger oxidative stress and can cause tissue or cell death. Hyperuricemia can also stimulate the RAS system, causing an increase in blood pressure in the glomerular capillaries and an increase in capillary hydrostatic pressure. Bowman's space edema is a protective form to prevent glomerular injury due to these conditions (10,20).

The administration of allopurinol therapy in rat group B showed a better histopathological picture of the renal glomeruli compared to group A which was induced with hyperuricemia without being given therapy. Allopurinol is a drug that has been available for more than 40 years (29). Allopurinol can be used for uric acid therapy. The mechanism of action of allopurinol is as an inhibitor of the xanthine oxidase enzyme, where this enzyme plays a role in the process of urate formation through the conversion of hypoxanthine to xanthine and uric acid, so that with this inhibition, the drug can reduce uric acid levels (30).

In the practical use of allopurinol for uric acid patients, the results are still often suboptimal and the dosage is still debated, especially for allopurinol therapy for patients with kidney disease. There is a complex relationship between serum urate and kidney function, where the kidneys play an important role in the excretion of uric acid and hyperuricemia is associated with chronic kidney disease (29). Allopurinol as a uric acid-lowering drug is excreted mainly through urine with the role of the kidneys. The use of allopurinol as uric acid therapy together with pre-existing kidney disorders can trigger the accumulation of allopurinol waste due to the inability of the body to excrete it properly. This accumulation can trigger acute toxicity due to the accumulation of metabolic waste from allopurinol in the body (31).

In Rahmah *et al*.'s study (32), it was found that allopurinol consumed by individuals with a prior history of kidney disorders can cause side effects on the kidneys. Based on the histopathological research conducted by Lestari *et al.* (17), it is known that allopurinol has a nephrotoxic effect, where from the allopurinol induction experiment carried out on DDY Strain Male mice, it was concluded that the higher the dose given, the more severe the kidney tissue damage that occurred in the mice. In this study, allopurinol therapy was given after the rats were induced into a hyperuricemic condition. Meanwhile, hyperuricemia can trigger inflammation through stimulation of the immune system activity. This pro-inflammatory condition will cause impaired kidney function, so allopurinol therapy may not be optimal. This is evidenced by the results of group B, which had worse results compared to the therapy results from the rat group given black garlic.

Rat groups C, D, and E were groups of rats that received black garlic therapy for seven days, after previously being induced with hyperuricemia by being given a high-purine diet for 14 days. Each of these groups received black garlic therapy doses of 240 mg/day, 480 mg/day, and 960 mg/day, respectively. The best results were obtained at the lowest dose given in this study, which was 240 mg/day. Then the trend of results experienced a decrease in protective effects with higher doses. The cause that was considered to underlie the results of black garlic therapy was related to the toxic nature of the organosulfur compounds contained in black garlic if given excessively. Based on research literature on diallyl disulfide (DADS), which is an example of an organosulfur compound, it is known

that this compound can provide a protective effect at low doses but can have a toxic effect at high doses (33). This is also in line with the results of research conducted by Asih *et al*. (22), where the administration of black garlic extracts at various doses showed good results in preventing a decrease in the quality of rat spermatozoa after exposure to cigarette smoke at a lower dose of black garlic, which was 500 mg/kgBW. Meanwhile, at the highest dose given in the study, which was 1000 mg/kgBW, the results were not better than the 500 mg/kgBW dose. These results are possibly due to excessive antioxidant levels at the dose of 1000 mg/kgBW. Excessive antioxidant content can lead to imbalance and trigger a pro-oxidant antioxidative stress condition that has the potential to cause cell damage (34).

The superior efficacy of the 240 mg/day dose can likely be attributed to an optimal balance between antioxidant activity and potential toxicity. Higher doses may induce a pro-oxidant state, as excessive antioxidants can disrupt cellular homeostasis (35). This disruption occurs when antioxidant levels surpass the cell's capacity to maintain redox balance, leading to oxidative stress rather than protection (36). Research has shown that excessive antioxidant intake can impair mitochondrial function, alter signaling pathways, and even promote cell death through mechanisms such as oxidative damage to lipids, proteins, and DNA (37). In the case of black garlic, its rich content of organosulfur compounds, including S-allyl cysteine, may provide protective effects at moderate doses but could become harmful when consumed in excess (18). This highlights the importance of dosage optimization in therapeutic interventions, where insufficient doses may be ineffective, while excessive doses could compromise cellular integrity, diminishing health benefits or causing adverse effects.

The observed protective effect of black garlic at lower doses may be attributed to its ability to modulate oxidative stress and inflammatory pathways. Future research should explore the molecular mechanisms underlying these effects and evaluate the long-term safety of black garlic supplementation in clinical settings. The observed protective effect of black garlic at lower doses may be attributed to its ability to modulate oxidative stress and inflammatory pathways. Future research should explore the molecular mechanisms underlying these effects and evaluate the long-term safety of black garlic supplementation in clinical settings. Moreover, it would be beneficial to investigate the optimal dosage range in human subjects, as well as its potential interactions with conventional therapies for hyperuricemia and kidney disease. This will help determine whether black garlic can be integrated as a complementary treatment option in preventing kidney complications.

While the protective effects of black garlic are evident in this animal model, further studies are needed to translate these findings to human populations. Additionally, the long-term safety of black garlic supplementation, particularly at higher doses, requires further investigation to prevent potential pro-oxidative effects. Given its accessibility and natural origin, black garlic could be included in dietary guidelines for populations at risk of hyperuricemia and kidney disease. Future public health initiatives could focus on promoting black garlic as part of a preventive diet for chronic kidney disease.

Implications for Public Health

The findings that black garlic supplementation can protect against glomerular damage in hyperuricemic conditions suggest it may have utility as a preventive measure against kidney complications, especially in populations at risk of hyperuricemia and kidney disease. This is relevant for public health efforts to reduce the burden of chronic kidney disease. With its anti-hyperuricemic and antioxidant effects, black garlic may offer a complementary or alternative therapy for managing elevated uric acid levels, alongside or in place of conventional drugs like allopurinol. This expands treatment options, which is beneficial from a public health perspective.

The study highlights the potential health benefits of functional foods like aged garlic extracts. Public health initiatives could leverage such findings to promote the consumption of functional foods as part of a preventive healthcare strategy. The findings indicate that while low doses of black garlic may be protective, higher doses could have adverse effects. This underscores the importance of proper dosing guidance for functional foods/nutraceuticals from a public health standpoint.

CONCLUSION

Black garlic provides protective effects on glomerular histopathology in hyperuricemic rats, with the 240 mg/day dose being the most effective. These results suggest potential use for black garlic in preventing kidney complications in hyperuricemia.

AUTHOR'S CONTRIBUTION STATEMENT

All authors contributed equally to the concept and design of this study.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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