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# Hypolipidemic Efficacy of *Achillea millefolium* L. Extract Against Diet-Induced Hyperlipidemia in Male Albino Rats

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## ABSTRACT

*Achillea millefolium (commonly known as yarrow) has demonstrated promising health benefits, including potential protective effects against heart disease and making it a valuable candidate for natural therapeutic applications* .The objective of this study was to evaluate the lipid-lowering efficacy of *Achillea millefolium* and its impact on lipid metabolism in normal albino rats, as well as those induced with hyperlipidemia through an 8-week regimen of a fat-enriched diet. This study comprised thirty-six male albino rats weighing between 200 and 280 g, which were randomly allocated into six groups. The negative control group was administered normal saline, while the treatment groups received *A. millefolium* extract (AME) at dosages of 100, 200, and 300 mg/kg orally. The positive control group was given simvastatin at 4 mg/kg orally, while the lipid control group received no intervention. All groups, excluding the negative control, were fed a fat-enriched diet for the duration of the study, during which the serum lipid profile was evaluated, including : total cholesterol (TC), triacylglycerol (TAG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C) levels. Blood samples were obtained at baseline and after four weeks of post-treatment for induced hyperlipidemia. The results of *A. millefolium* extract showed significantly raised levels of (HDL-C) while decreasing levels of (TAG), (LDL-C), (VLDL-C), and (TC), especially at a dosage of 300 mg/kg. According to results *A. millefolium* extract has a significant potential for becoming an effective treatment for hyperlipidemia.

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## INTRODUCTION

Hypercholesterolemia poses significant health risks and is commonly linked to increased mortality, hypertension, hyperlipidemia, insulin resistance, and glucose intolerance all of which are recognized cardiovascular risk factors that often coexist in individuals with obesity (Myśliwiec *et al*., 2024). The persistence of hypercholesterolemia leads to heightened oxidative stress, which facilitates the development of atherosclerosis and coronary artery disease (Myszko *et al*., 2025). Cholesterol in blood serum is transported by lipoproteins, which are primarily categorized into five types based on the size of cholesterol-lipoprotein complexes: High-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and chylomicrons (Lütjohann *et al*., 2023). Pharmacological control of cholesterol levels has significantly reduced the risk of atherosclerosis and associated disorders (Xiao *et al*., 2023). Statin drugs are known to lower LDL cholesterol by 20-35% because of fluvastatin and simvastatin which, in turn, reduces heart disease risk by 30-35%. Their primary action is in the liver, which is the site of synthesis and degradation of cholesterol. However, the long term of it use may increase the risk of adverse effects such as myopathy, they do not work in all cases (Banach *et al*., 2024). Moreover, the adverse effects associated with therapeutic drugs, such as myopathy, hepatic damage, and potential drug-drug interactions, have been recorded. This increases the demand for other natural alternatives to safely manage cholesterol levels (Ma *et al*., 2024). Global interest in herbal remedies has been on the rise, traditional medicinal plants demonstrating hypercholesterolemic effects may provide a significant resource for developing a new oral hypolipidemic drug or as an adjunctive dietary supplement to existing therapies. Futhermore, Ethnopharmacological studies indicate that about 1200 plants are employed in traditional medicine for

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their hypolipidemic effects, including *Achillea millefolium* (Tusheema *et al*., 2021). More importantly, *A. millefolium* is a traditional herb from the Asteraceae family, employed for millennia due to its wound-healing capabilities, which assisting in the control of hemorrhages and infections. The plant is believed to provide a therapeutic impact on the gastrointestinal system and acting as a detoxifier through the skin and urinary system. Herbalists use it to manage hypercholesterolemia and hypertension (Afshari *et al*. 2018). Therefore, the study aimed to evaluate the effectiveness of *A. millefolium* extract in reducing elevated lipid levels caused by a high-fat diet in male albino rats.

## MATERIALS AND METHODS

*Animals*

Several of male albino rats (aged 14-18 weeks) weighing 200-280 g were housed in conditioned cages indoors in a room (22-25°C) obtained from the laboratory animal colony, Cancer Research Center, Baghdad, Iraq. The rats were maintained under standard conditions and in accordance with university guidelines.

*Preparation of plant extract*

The aerial parts of *A. millefolium* were powdered by grinding. The extract of the plant was prepared as follows: 60 g extract with 400 ml of ethanol 70% using a Soxhlet apparatus until the extraction was complete. A rotary evaporator condensed the extract at 40 °C, yielding a yellowish dark green colored residue known as the extract. 3.7 g of the extract was collected from 60 g of the ground plant.

*Acute toxicity*

Experiments were conducted on the extract of *A. millefolium* utilizing the 'Up-and-Down' approach. The investigation was conducted on male albino rats, with single doses administered at 50, 100, 200, 300, 600, and 2000 mg/kg body weight (the limit test). The experiment adhered to the protocols specified in OECD (Organization for Economic Cooperation and Development) guideline no. 425 (OECD, 2001). Five male rats were used at each dosage level. Each rat was weighed separately, and the extract, diluted in distilled water, was administered orally via gavage in volumes adjusted to body weight. Following administration, the rats were meticulously observed for 14 days to detect any indications of acute toxicity. This observation period included the assessment of mortality, behavioral changes, and modifications in respiratory or digestive systems. Physical and morphological changes were monitored, including changes in eye color, skin condition, diarrhea, lethargy, tremors, convulsions, and episodes of coma or sleep.

*Chemicals*

Kits for biochemical analysis of serum total lipids (Catalog No. PCI/TL-MAK074), triacylglycerol (Catalog No. PCI/TG- MAK266), total cholesterol (Catalog No. PCI/TC- MAK043), and HDL-C (Catalog No. PCI/HDL-MAK045) were purchased from the Pharmaceutical and Chemical Institute, Baghdad, Iraq.

*Preparation of standard and high-fat diets (HFD)*

We devised the high-fat diet in accordance with recognized guidelines from prior research. The composition comprised protein (365 g), lard (310 g), casein (210 g), cholesterol (10 g), vitamins and minerals (60 g), D1-methionine (3 g), yeast powder (1 g), and sodium chloride (1 g). We meticulously amalgamated all constituents utilizing a mechanical mixer. The mixture was subsequently shaped into pellets, with distilled water added as necessary, and ultimately dried at ambient temperature in shaded settings (Nurul *et al*., 2022).

*Hypolipidemic activity of* Achillea millefolium *extract (AME) against high-fat diet-induced hyperlipidemia experimental design*

In this study, all animal groups received the high-fat diet for an 8-week period except negative control fed a standard or normal diet. This study was conducted to observe treating the incidence of hyperlipidemia by the application of *Achillea millefolium* extract (AME) and comparing the effect of the plant extract with simvastatin (4 mg/kg B.W. p.o.) as a positive control and a normal control that was given distilled water. Serial assessments of lipid parameters were conducted at baseline Week 0, Week 4, and Week 8 to comprehensively evaluate both disease progression and therapeutic response.

Randomly divided into six groups (6=n/group) each of which received the following treatment for 8 weeks: (i) Group I (negative control) was administered distilled water and a standard diet, (ii) Group II (lipid control group) fed on high-fat diet + distilled water (untreated pathological control), (iii) Group III fed on high-fat diet + 100 mg/kg B.W. of AME, (iv) Group IV fed on high-fat diet + 200 mg/kg B.W. of AME, (v) Group V fed on high-fat diet + 300 mg/kg B.W. of AME, (vi) Group VI (positive group) fed on high-fat diet + 4mg/kg B.W. p.o. of the drug (simvastatin).

*Blood sampling and lipid profile analysis*

Blood samples were drawn at different intervals (0, 4 and 8 weeks) along the experiments from anesthetized animals (intraperitoneal injection of 35 mg/kg of sodium

pentobarbital) into tubes containing heparin, using the cardiac puncture technique.

Serum was immediately separated by centrifugation at 3000 rpm for 15 min, then serum samples were stored at -20 °C until use.

The analytical kit (Sigma Aldrich Chemical Ltd., Germany) were used for the estimation of total cholesterol (TC), triacylglycerol (TAG), high-density lipoprotein cholesterol (HDL-C). The low-density lipoprotein cholesterol (LDL-C) was calculated by the William formula (William, 2020): LDL-C = TC–HDL-C–TG/5, while the Very low-density lipoprotein cholesterol (VLDL-C) was calculated by dividing serum TAG by five (Friedewald *et al*., 1972): VDL-C=TG/5

*Statistical analysis*

The statistical analysis of the data was performed base on either a one-way or two-way analysis of variance (ANOVA) using a significance level of $p < 0.05$. Specific group differences were determined using the test of significant difference (LSD) (Snedecor and Cochran, 1989).

## RESULTS

*Acute toxicity*

When rats were given doses of 50, 100, 200, 300, 600, and 2000 mg/kg of the ethanolic extract of *A. millefolium*, no mortality or observable adverse effects were recorded during the 14-day study. This suggests that the extract is likely safe at these doses, and the oral LD50 is estimated to be greater than 2000 mg/kg in rats.

*Lipid profile*

Table I shows effect of different doses of AME on lipid profile of rats fed on high fat diets for 8 weeks. There were no significant (P>0.05) differences in serum mean values of total cholesterol (TC) in zero week in all experimental groups when compared to each others. A significant (P<0.05) elevation in mean serum total cholesterol (TC) concentrations was observed in the lipid control group (high-fat diet) at 4 weeks (259.39 ± 1.80 mg/dL) and 8 weeks (316.48 ± 1.63 mg/dL), compared to the negative control group. However, the groups treated with 100, 200, and 300 mg/kg of AME showed significantly lower TC levels ($P < 0.05$) compared to the lipid control group at both 4 and 8 weeks. No statistically significant differences were observed between the 100 and 200 mg/kg groups at either time point.

Also, the oral administration of the positive control group (simvastatin 4 mg/kg) and 300 mg/kg of AME produced statistically significant (P<0.05) reductions in serum cholesterol concentrations . Total cholesterol values for these treatment groups were measured at 8 weeks (117.52 ± 1.42 mg/dL) and (116.13±0.43 mg/dL) respectively, compared with lipid control group, these therapeutic interventions effectively restored serum cholesterol levels to near - normal values, closely approximating those observed in the negative control group (104.08±1.04) mg/dL.

*TAG*

There were no significant (P>0.05) differences in the mean values of serum TAG concentration between groups during the pretreated period (0 week). Furthermore, the values of TAG tended to reduction significantly (P<0.05) in the positive control group ( simvastatin 4 mg/kg) and AME (100, 200 and 300 mg/kg groups) after 8 weeks with mean values of (70.15±1.76 mg/dL), (92.85±1.91 mg/dL), (85.35±1.78 mg/dL) and (70.27±0.88 mg/dL) respectively, compared with lipid control (129.66±2.49 mg/dL). While no significant differences in this parameter were observed in 300 mg/kg group comparing to positive control group ( simvastatin 4 mg/kg ) in the same period of treatment, compared to the negative control group (68.13±1.51 mg/dL) .

*HDL-C*

A time-dependent, statistically significant ($P < 0.05$) decrease in mean HDL-C concentrations was observed in the lipid control group (high-fat diet) at 4 weeks (24.16±0.29 mg/dL) and 8 weeks (20.45±0.93 mg/dL), compared to the negative control group. However, the groups treated with 100, 200, and 300 mg/kg of AME showed significantly higher HDL-C levels ($P < 0.05$) compared to the lipid control group at both 4 and 8 weeks. No statistically significant differences were observed between the 200 mg/kg group and positive control group (simvastatin 4 mg/kg) at either time point.

Also, the oral administration of AME (300 mg/kg) produced statistically significant (P<0.05) increase in serum HDL-C values at 8 weeks (34.37±1.54 mg/dL) compared with lipid control group, these therapeutic interventions effectively increased and restored serum HDL-C levels to near normal values, closely approximating those observed in the negative control group (34.94±1.62mg/dL).

*LDL-C*

The effects of a high-fat diet with AME , on serum LDL-C concentrations across all experimental groups are shows in Table I. During the pretreatment period (0 week), no statistically significant differences ($P > 0.05$) in serum LDL-C concentrations were observed among any of the experimental groups.

**Table I. Effect of oral administration of *Achillea millefolium* extract (AME) on blood serum lipid profile of high fat diet induced hyperlipidemic male albino rats.**

| Lipid parameters | AME administered for(weeks) | Group I (n=6) Negative control | High fat diet | | | | |
|---|---|---|---|---|---|---|---|
| | | | Group II (n=6) Lipid control | Group III (n=6) AME 100 mg /kg B.W.) | Group IV (n=6) AME 200 mg /kg B.W. | Group V (n=6) AME 300 mg /kg B.W. | Group VI (n=6) simvastatin 4 mg /kg B.W. |
| TC (mg/dl) | 0 | 103.06±1.04 A a | 104.18±1.11 A c | 103.5±0.93 A c | 102.88±0.99 A c | 103.93±1.03 A b | 104.08±1.04 A b |
| | 4 | 103.06±1.04 D a | 259.39±1.80 A b | 221.42±1.80 B a | 218.75±1.43 B a | 192.89±1.8 C a | 186.75±1.67 C a |
| | 8 | 103.19±1.11 C a | 316.48±1.63 A a | 195.15±1.65 B b | 172.15±1.42 B b | 117.52±1.88C bc | 116.13±0.43C bc |
| TAG (mg/dl) | 0 | 67.50±1.37A a | 68.95±0.95 A c | 67.64±1.58 A c | 67.30±1.71 A c | 67.42±0.56 A c | 66.60±1.35 A c |
| | 4 | 67.35±1.42 E a | 115.58±1.78 A b | 108.98±1.77 B a | 96.87±0.83 C a | 88.76±1.21 D a | 86.43±0.82 D a |
| | 8 | 68.13±1.52D a | 129.66±2.49 A a | 92.85±1.91 B b | 85.35±1.78 C b | 70.27±0.88 D b | 70.15±1.76 D b |
| HDL-C (mg/dl) | 0 | 34..76±1.51 A a | 33.16±1.42 A a | 33.39±0.93 A a | 34.06±1.13 A a | 33.82±0.71 A a | 33.53±0.78 A a |
| | 4 | 33..28±0.90 A a | 24.16±0.29 B b | 25.39±0.77 B b | 26.06±1.17 C c | 27.55±0.65 C b | 25.52±0.27 C c |
| | 8 | 34.94±1.62 A a | 20.45±0.93 A c | 28.37±1.60 B c | 29.44±1.12 B b | 34.37±1.54 A a | 30.31±1.94 B b |
| LDL-C (mg/dl) | 0 | 19.68±0.51 A a | 19.51±1.33 A a | 19.27±1.47 A a | 18.92±1.23 A a | 19.22±1.37 A a | 18.76±0.89 A a |
| | 4 | 18.44±0.53 D a | 64.51±1.64 A b | 75.33±1.94 B c | 70.92±1.12 B c | 64.51±1.58 C c | 62.56±0.71 C c |
| | 8 | 19.21±1.36 C a | 86.92±1.87 A c | 63.27±1.15 B b | 58.96±1.84BC b | 24.13±1.42 C b | 21.09±1.89 C b |
| VLDL-C(mg/dl) | 0 | 13.50±0.44 A a | 13.79±0.14 A c | 13.52±0.92 A a | 13.46±0.44 A c | 13.49±0.31 A b | 13.32±1.15 A b |
| | 4 | 13.47±0.59 E a | 23.12±0.78 A b | 21.80±1.71 B a | 19.37±0.63 C a | 17.75±1.22 D a | 17.29 ±1.12 D a |
| | 8 | 13.32±1.16 C a | 25.93±0.39 A a | 18.57±1.01 B b | 17.07±0.54 B b | 14.05±0.75 C b | 14.03±0.96 C b |

TC, Total cholesterol; TAG, triacylglycerol, HDL-C, High density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; VLDL-C, very-low-density lipoprotein-cholesterol. Capital letters horizontally represent significant difference between groups (p<0.05) vs. control. Small letters vertically represent significant difference within group (p<0.05) vs. zero time. Values are expressed as mean ± SEM. LSD for TC=2.86; TAG=3.78; HDL-C=1.61; LDL-C=3.78; VLDL-C=0.78

A significant (P<0.05) elevation in mean serum LDL-C concentrations was observed in the lipid control group (high-fat diet) at 4 weeks ( 64.51±1.64 mg/dL) and 8 weeks (86.92±1.87 mg/dL), compared to the negative control group. Indicates a statistically significant ($P < 0.05$) reduction in serum LDL-c concentration following 4 weeks of administration of either AME or positive group (simvastatin 4 mg/kg) when compared to lipid group. At 8 weeks, AME treatment (100, 200, and 300 mg/kg) significantly (P<0.05) reduced LDL-C to 63.27±1.15, 58.96±1.84, and 24.13±1.42 mg/dL, respectively, versus the lipid control group (86.92±1.87 mg/dL).

During the same treatment period, the 300 mg/kg group (24.13±1.42 mg/dL) showed no significant difference (P<0.05) in this parameter compared with the positive control group (simvastatin 4 mg/kg) (21.09±1.89 mg/dL), both showed less significant differences (P > 0.05) relative to the negative control group (19.21 ± 1.36 mg/dL).

*VLDL-C*

During the pretreatment period (0 week), no statistically significant differences (P > 0.05) in serum VLDL-C concentrations were observed among any of the experimental groups.

Furthermore, the values of VLDL-C tended to reduction significantly (P<0.05) in the AME (100, 200 and 300 mg/kg groups) and positive control group ( simvastatin 4 mg/kg) after 8 weeks with mean values of (70.15±1.76 mg/dL), (18.57±1.01 mg/dL), (17.07±0.54 mg/dL), (14.05±0.75 mg/dL) and (14.03±0.96 mg/dL) respectively compared with lipid control ( 25.93±0.39 mg/dL). While no significant differences(P<0.05) in this parameter were observed in the 300 mg/kg group compared to the positive control group ( simvastatin 4 mg/kg ) in the same period of treatment**,** both showed no significant differences (P > 0.05) relative to the negative control group (13.32±1.16 mg/dL) (Table I).

## DISCUSSION

Numerous detrimental consequences have been linked to the hypolipidemic medications currently accessible. These synthetic pharmaceuticals may result in adverse effects including hyperuricemia, gastrointestinal disturbances (such as diarrhea and nausea), myositis, gastric irritation, flushing, xerosis, and impaired liver function. Given these constraints, there is interest in developing herbal medications as alternative therapies for hyperlipidemia, as they generally provide therapeutic advantages with reduced adverse effects. In this context,

herbal remedies offer a promising pathway for the advancement of safer antihyperlipidemic treatments. Experimental models of hyperlipidemia in rats, produced by high-fat diets or triton administration, have been established as dependable *in vivo* systems for assessing the efficacy of lipid-lowering agents (Wong *et al*., 2022).

In the present study, the ethanolic extract of *A. millefolium*, there were no deaths or harmful effects seen during the 14-day study, indicating that mean it is likely safe (Georgieva *et al*., 2015). The results were obtained from high-fat- diet animals before receiving AME or drug therapy, revealing a higher serum concentration (mg/dl) of cholesterol as compared to the control animals. Conversely, there was a significant decline in HDL-C concentrations in high-fat diet animals. In the post-treatment period, serum TC, TG, LDL-c, and VLDL-C concentrations were significantly lower in the group that was given Achillea extract and drug in comparison with the untreated group. The lowest reduction in TC, TG, LDL-C, and VLDL-C concentration was determined in the group (300 mg/kg) and simvastatin in the treated group, while no statistically significant difference between the groups. This finding is in agreement with Rezaei *et al*. (2020) who found *A. millefolium* administration for 28 days significantly improved a number of health indicators in rats with streptozotocin-induced diabetes. Rats which received extract had significantly higher levels of HDL cholesterol and significantly lower levels of total cholesterol, LDL cholesterol, triacylglycerol, liver enzymes, and blood glucose than the untreated control group.

The coenzyme a reductase is the most important enzymes in the process of cholesterol synthesis. Some of the key substances that can slow down this enzyme include cholesterol (which acts through negative feedback), glucagon, cortisol, and cholesterol-lowering medications like simvastatin and atorvastatin (Nkeh *et al*., 2024). The hypolipidemic activity of *A. millefolium* extract may be due to presence of phenols, steroids, tannins, saponins, glycosides, flavonoids, and alkaloids (Kumar *et al*., 2011; Georgieva *et al*., 2015). Saponins can inhibit cholesterol absorption directly and indirectly in the gut, leading to reduction in serum cholesterol, serum triacylglycerol, and total bile acids by increasing the excretion of total cholesterol, serum and bile acids in feces (Bogoriani *et al*., 2020). Also contains unsaturated fatty acids with a high nutritional value, including oleic acid, linoleic acid, and linolenic acid (Dolly *et al*., 2020). Besides, contains unsaturated fatty acids with a high nutritional value, including oleic acid, linoleic acid, and linolenic acid (Dolly *et al*., 2020). They are considered potent antioxidants with a single double bond in their structure. Moreover, a decrease in serum lipids, including cholesterol, and an increase in HDL-c levels can be attributed to the ability of essential fatty acids to regulate enzymes involved in glycolysis and lipolysis, thereby modulating lipid metabolism. Alkaloids are substances that inhibit cholesterol synthesis (Mohd *et al*., 2017).

One of bioactive components in *A. millefolium* is its polyphenolic compounds, which play a critical role as antioxidants. These compounds effectively scavenge free radicals and reduce membrane lipid peroxidation, thereby lowering the risk of oxidative stress-related diseases such as myocardial infarction and atherosclerosis (Morillas-Ruiz *et al*., 2006; Silva *et al*., 2007*)*.

Craig (2004) found that *A. millefolium* extract contains betaine (trimethylglycine), which plays a critical role in lipid metabolism by serving as a methyl donor in the conversion of homocysteine to methionine, a process essential for hepatic VLDL synthesis and fat export. This may lead to a decrease in the removal of VLDL from the circulation and an increase in serum VLDL and cholesterol levels (Feingold, 2022).

In addition, certain alkaloids a class of nitrogen-containing bioactive compounds have been shown to inhibit LDL-c oxidation in vitro and exhibit significant hypolipidemic effects *in-vivo*. These findings suggest that alkaloids and flavonoids may contribute to the prevention and treatment of atherosclerosis (Zhao and Shi-Liang, 2018).

In other study, Yarrow (*A. millefolium*) contains a variety of bioactive compounds that contribute to its medicinal properties. Among these, the alkaloid-like compound achilleine stands out for its potential role in lowering blood lipid levels through reduce the accumulation of lipids in cells (Németh and Bernáth, 2008).

## CONCLUSION

The current research indicated that a dosage of 300 mg/kg B.W. of *A. millefolium* extract over a period of 4 weeks effectively induced a hypolipidemic effect in rats subjected to a high-fat diet, evidenced by a reduction in blood total cholesterol (TC), triacylglycerol (TAG), low-density lipoprotein cholesterol (LDL-c), and very-low-density lipoprotein cholesterol (VLDL-c), alongside an elevation in high-density lipoprotein cholesterol (HDL-c) levels.

## DECLARATIONS

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*IRB approval*

The manuscript was evaluated and approved by the scientific committee of the department of physiology and pharmacology at the College of Veterinary Medicine at the University of Baghdad ((No. 3650 dated 07/10/2023).

*Ethical approval*

The study protocol used in this study were thoroughly reviewed and approved by the Scientific Committee of the College of Veterinary Medicine at the University of Baghdad (Protocol No. P.G/1128), ensuring full compliance with ethical standards for animal welfare.

*Novelty statement*

The aim of this study is to investigate the potential therapeutic treatment effects of *A. millefolium* extract on hyperlipidemia, a prevalent condition that has been linked to various health complications. By conducting the research on male albino rats, the aim is to provide preliminary evidence on the dosage required for effective treatment. This study sets itself apart by addressing the need for alternative treatments for hyperlipidemia and by providing insight into the potential benefits of *A. millefolium* extract in addressing this health issue.

*Generative AI and AI-assisted technology statement*

The author declare that no generative AI or AI assisted technologies was used in this manuscript.

*Statement of conflict of interest*

The authors have declared no conflict of interest.

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