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Comparing the Effects of a Course of Endurance and Resistance Training Combined with Sumac Supplementation on Serum Levels of SIRT3, SIRT4, and AMPK in a Rat Model of Alzheimer's Disease

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ABSTRACT

Background and Objective: Alzheimer's disease (AD) is the most common type of dementia that is progressively associated with memory loss. Given that free radicals and sirtuins are factors involved in the occurrence of AD, the aim of this study was to compare the effect of 12 weeks of endurance and resistance training combined with sumac supplementation on serum levels of SIR3, SIR4, and AMPK in AD-induced rats.

Methods: In this experimental study, 49 rats aged 8-10 weeks and weighing 200±30 g were randomly divided into seven groups of 7, including healthy control group, AD-induced rats, AD-induced rats under sumac supplement, AD-induced rats under endurance training, AD-induced rats under endurance training and sumac supplement, AD-induced rats under resistance training, and AD-induced rats under resistance training and sumac supplement. Trimethyltin chloride was used intraperitoneally to induce AD. The maze test was used to measure memory. Sumac was added to the food of the samples at a ratio of 10% and was freely available to them. Endurance training was performed by swimming in a special mouse pool and resistance training by climbing a ladder with weights attached to the tails of the rats for 12 weeks. Then, serum levels of SIR3, SIR4, and AMPK were evaluated and compared by ELISA.

Findings: Twelve weeks of endurance training significantly increased SIR3 (0.87±0.18) ($p<0.002$) and SIR4 (0.86±0.08) ($p<0.001$) in the AD-induced group under endurance training compared to the AD-induced group; but there was no significant effect on AMPK (4.66±0.13). Twelve weeks of resistance training significantly increased SIR3 (0.77±0.14) ($p<0.036$) and SIR4 (0.80±0.08) ($p<0.029$) in the AD-induced group under resistance training compared to the AD-induced group; but there was no significant effect on AMPK (4.40±0.24). Adding sumac to the endurance training program did not have a significant effect on the levels of SIR3 (0.90±0.13) and SIR4 (0.89±0.11) in the AD-induced group under endurance training compared to the AD-induced group; but there was a significant effect on AMPK (0.99±0.30) ($p<0.05$). Adding sumac to the resistance training program did not cause significant changes in the levels of SIR3 (0.77±0.11) and SIR4 (0.86±0.15) in the AD-induced group under resistance training compared to the AD-induced group; but there was a significant effect on AMPK (5.93±1.32) ($p<0.04$).

Conclusion: The results of the study showed that both endurance and resistance training significantly increased the levels of SIR3 and SIR4, and adding sumac to the endurance or resistance training program had no significant effect on the levels of SIR3 and SIR4; however, both exercises had a significant effect on AMPK.

Keywords: *Alzheimer's Disease, Endurance Training, Resistance Training, Sumac, Sirtuin, Adenosine Monophosphate Kinase.*

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Introduction

Alzheimer's disease (AD) is a fatal progressive neurodegenerative disease characterized by memory loss and multiple cognitive impairments (1). Despite extensive research to understand this complex disease, the exact pathophysiology of the disease is not fully understood. Given that free radicals are one of the factors involved in the development of AD, the use of medicinal plants has attracted much attention due to their antioxidant properties (2). Among these plants, sumac (Rhus coriaria L.) has potential antioxidant, anti-inflammatory, and neuroprotective activities (3).

Another inducing agent is Trimethyltin chloride, which is abundant in soil, tap water, landfill leachate, and marine ecosystems (4) and is shown to cause mental confusion, memory problems, and seizures after exposure (5). Systemic administration of TMT in rodents induces clinical signs associated with AD and specifically causes damage to the hippocampus in the central nervous system (CNS) (6). Research has shown that TMT-induced neurodegeneration is associated with dysregulated metabolism, which impairs synaptic function in neurodegeneration (7).

Another modulator of metabolic pathways and cellular stress responses are the sirtuins (8). Sirtuin3 activity is increased during exercise, leading to increased energy metabolism. In response to the signals of diet or exercise, SIRT3 increases the activation of AMP-activated protein kinase. Reduced levels of SIRT3 in skeletal muscle can lead to mitochondrial dysfunction and increased oxidative stress. In addition, SIRT4 functions as a metabolic regulator, including regulation of lipid and glucose metabolism and oxidative stress in mitochondria via NAD+ (9). It seems that phosphorylation increases amyloid precursor protein (ABP), amyloid beta and oxidative stress and negatively regulates or reduces sirtuin levels (10).

Mitochondrial dysfunction and neuronal hyperexcitability are two age-related changes in AD pathogenesis; sirtuin levels are significantly reduced, resulting in increased mitochondrial protein acetylation in brain cells during aging (11). On the other hand, increased Aβ accumulation following AD can reduce AMPK activity. These factors disrupt mitochondrial DNA function of neurons and ultimately lead to cell death (12). Despite the fact that AMPK has a positive effect on the health of the organism, evidence also suggests its involvement in the pathogenesis of AD. AMPK appears to link energy metabolism to synaptic plasticity, which in turn suggests that energy deficiency is associated with an abnormality in synaptic transmission and memory impairment (13).

Physical activity can prevent cognitive decline and dementia (14). Aerobic and resistance training may delay and prevent cognitive decline in older adults with AD; therefore, physical activity appears to be one of the most promising, effective, and cost-effective ways to prevent and delay cognitive decline in patients with AD (15).

Given the increasing incidence of AD, it seems best to use treatment methods that can at least reduce the financial burden of treatment and, on the other hand, help improve the health of affected individuals with better efficiency. As mentioned, the use of antioxidant supplements along with physical exercise may be one of these ways to improve AD, although its physiological mechanisms are not well understood. Therefore, the present study was conducted to compare the effect of 12 weeks of endurance and resistance training combined with sumac supplementation on the serum levels of mitochondrial sirtuins (SIRT3, SIRT4) and AMPK in AD-induced rats.

Methods

After approval by the Ethics Committee of the Islamic Azad University, Borujerd Branch with the code IR.IAU.B.REC.1402.005, this laboratory study was conducted on 49 rats with a mean age of 8 to 10 weeks

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and a mean weight of 200±30 grams. During the research period, the samples were kept in an environment with a temperature of 20-24ºC, a humidity of 45-55%, and a 12-hour light/12-hour dark cycle. They also had free and sufficient access to water and food. After being transferred to the laboratory and getting familiarized with the new environment and the training method for a week, the samples were randomly divided into 7 groups of 7: healthy control, AD-induced rats, AD-induced rats+sumac supplement, AD-induced rats+endurance training, AD-induced rats+endurance training+sumac supplement, AD-induced rats+resistance training, and AD-induced rats+resistance training+sumac supplement. To induce AD, 8 mg/kg of TMT (Sigma-Aldrich) was injected intraperitoneally into animals along with 200 µL of normal saline as a solvent (16). The maze test (a short-term spatial memory test) was used to evaluate memory (17). Then, sumac was mixed with the animal food at a ratio of 10% and freely available to the samples (18).

Endurance and resistance training program: The training period was 12 weeks, 5 days a week (19). Endurance swimming training was performed in a special rat pool measuring 80×50×50 cm, equipped with a wave machine and water temperature of 30 to 33°C. Resistance training was performed by climbing a ladder 1 m long with 26 steps and an angle of 85° to the ground with weights attached to the rats' tails. Each training session consisted of 3 sets of 4 repetitions, with 30 to 60 seconds of rest between each repetition and 120 to 150 seconds between each set (Table 1) (20). The intensity of the training was 50-60% of the maximum oxygen consumption.

Table 1. Endurance and resistance training program

	Endurance training program		Resistance training program		
Week	**Duration (minutes)**	**Interval between training (hours)**	**Weight percentage**	**Interval between each repetition (seconds)**	**Interval between each set (seconds)**
1	15	24	50	30	120
2	20	24	60	30	120
3	30	24	70	30	120
4	40	24	80	30	120
5	50	24	90	30	120
6	60	24	100	30	120
7	60	24	105	30	120
8	60	24	110	30	120
9	60	24	120	50	140
10	60	12	130	50	140
11	60	12	140	60	150
12	60	12	150	60	150

Biochemical evaluation: 48 hours after the training program, the samples were anesthetized with sodium pentobarbital gas (manufactured by Sigma-Aldrich) and a 5-cc blood sample was collected from the heart. Then, the serum was separated by centrifugation at 1000 rpm. To measure the level of SIRT3, an ELISA kit (made in England) with a sensitivity of less than 0.058 ng/ml was used, and to measure the level of SIRT4 and AMPK, an ELISA kit (made in America) with a sensitivity of less than 0.124 ng/ml was used.

The Shapiro-Wilk test was used to examine the normality of the data distribution, the one-way analysis of variance test was used to examine the changes between groups, and the Tukey post hoc test was used to determine the differences between groups. Analyses were performed with SPSS software version 29, and $p<0.05$ was considered significant.

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Results

The results showed that the induction of AD caused a decrease in SIRT3 levels in all study groups compared to the control group (Figure 1). The data showed that both sumac consumption and endurance and resistance training can increase the SIRT3 variable, and endurance and resistance training along with sumac supplementation caused the greatest increase in this variable (Figure 1).

The results of one-way analysis of variance for SIRT3 showed a significant difference (33.33±1.31) between the study groups (p<0.0001). To examine the possible differences between the study groups, Tukey's post hoc test was performed, the results of which are shown in Table 2.

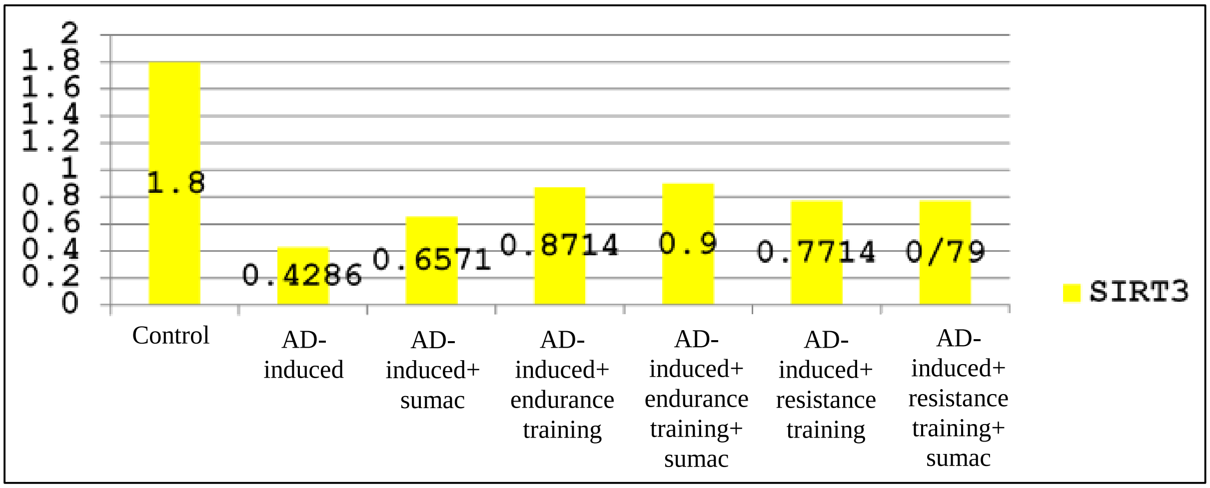

Figure 1. Mean SIRT3 in each of the different research groups

Table 2. Examining the existence of significant differences between different research groups for the SIRT3 variable using Tukey's post hoc test

Significance levels of groups	AD-induced +Resistance training +Sumac Supplement	AD-induced +resistance training	AD-induced+Endurance Training+Sumac Supplement	AD-induced +Endurance Training	AD-induced +Sumac Supplement	AD-induced
Control	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
AD-induced	0.048*	0.036*	0.001*	0.002*	0.047*	
AD-induced +Sumac Supplement	0.979	0.931	0.274	0.360		
AD-induced +Endurance Training	0.903	0.949	0.999			
AD-induced +Endurance Training+Sumac Supplement	0.820	0.886				
AD-induced +resistance training	0.999					

***Indicates significant difference between the study groups.**

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The results also showed that AD induction caused a decrease in SIRT4 levels in all study groups compared to the control group. The data showed that both sumac consumption and endurance and resistance training can increase the level of the SIRT4 variable, and endurance training combined with sumac supplementation causes the greatest increase in this variable (Figure 2).

The results of one-way analysis of variance for SIRT4 showed a significant difference (12.590±0.295) between the study groups ($p<0.0001$). To investigate the possible difference between the research groups, Tukey's post hoc test was performed, the results of which are shown in Table 3.

The results also showed that AD induction caused a decrease in AMPK levels in all study groups compared to the control group. The data showed that both sumac consumption and endurance and resistance training can increase the SIRT4 variable, and endurance training along with sumac supplementation caused the greatest increase in this variable (Figure 3).

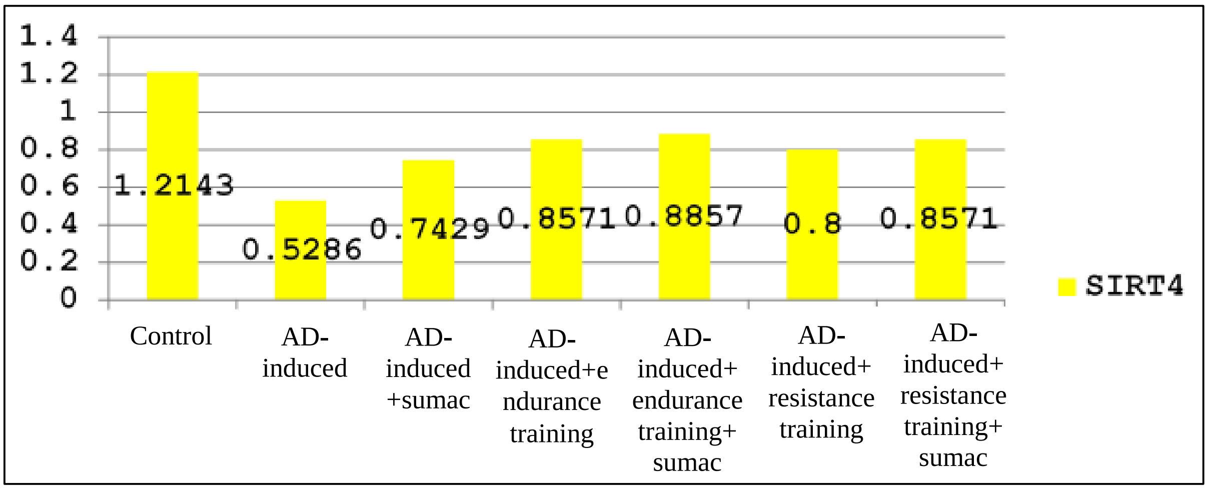

Figure 2. Mean SIRT4 in each of the research groups

Table 3. Examining the existence of significant differences between different research groups for the SIRT4 variable using Tukey's post hoc test

Significance levels of groups	AD-induced+ Resistance training+ Sumac Supplement	AD-induced+ resistance training	AD-induced+ Endurance Training+ Sumac Supplement	AD-induced+ Endurance Training	AD-induced+ Sumac Supplement	AD-induced
Control	0.001*	0.0001*	0.004*	0.003*	0.0001*	0.0001*
AD-induced	0.024*	0.029*	0.001*	0.001*	0.147	
AD-induced+ Sumac Supplement	0.976	0.992	0.591	0.540		
AD-induced+ Endurance Training	0.977	0.923	0.999			
AD-induced+ Endurance Training +Sumac Supplement	0.983	0.940				
AD-induced+ resistance training	0.999					

***Indicates significant difference between the study groups.**

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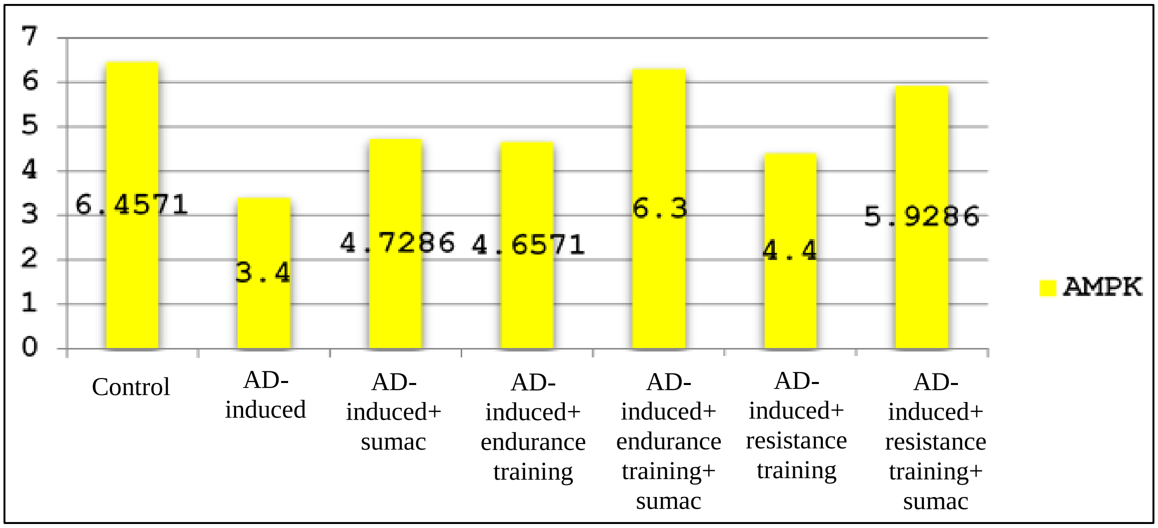

Figure 3. Mean AMPK in each of the different research groups

The results of one-way analysis of variance for AMPK showed a significant difference (9.179±8.260) between the study groups (p<0.0001). To examine the possible differences between the research groups, a Tukey post hoc test was performed, the results of which are shown in Table 4.

The results of one-way analysis of variance for the maze test showed a significant difference (123.7±0.95) between the groups (p<0.0001). The post hoc test showed that after the intervention period, the memory level in the AD-induced group was significantly different compared to the endurance training group, the AD-induced+sumac group, the endurance training+sumac group, and the control group (p<0.0001).

Table 4. Examining the existence of significant differences between different research groups for the AMPK variable using Tukey's post hoc test

Significance levels of groups	AD-induced+ Resistance training+ Sumac Supplement	AD-induced+ resistance training	AD-induced+ Endurance Training+ Sumac Supplement	AD-induced+ Endurance Training	AD-induced+ Sumac Supplement	AD-induced
Control	0.774	0.004*	0.999	0.0420*	0.023*	0.0001*
AD-induced	0.002*	0.447	0.0001*	0.0131	0.143	
AD-induced+ Sumac Supplement	0.570	0.995	0.050*	0.997		
AD-induced+ Endurance Training	0.858	0.871	0.045*			
AD-induced+ Endurance Training+ Sumac Supplement	0.890	0.009*				
AD-induced+ resistance training	0.04*					

***Indicates a significant difference between the study groups.**

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Discussion

The results of the present study showed that both endurance and resistance training significantly increased the levels of SIR3 and SIR4; but there was no significant effect on AMPK compared to the AD-induced group. Adding sumac to the endurance or resistance training program did not have a significant effect on the levels of SIR3 and SIR4; however, both exercises had a significant effect on AMPK.

The effect of physical exercise on SIRT3 abundance in human and rodent tissues is controversial, with reports suggesting that exercise does not systematically increase SIRT3. However, other studies conclude that regular periods of endurance training increase SIRT3 abundance in multiple tissues (21-23). Regardless of age, chronic endurance training is effective in improving SIRT3 expression in human skeletal muscle and serum. One study found that 8 or more weeks of endurance training can effectively increase SIRT3 expression in skeletal muscle and serum in individuals of all ages (24). In contrast, only a limited number of studies have examined the effect of resistance training on SIRT3 expression. One study in older adults showed that 12 weeks of resistance training increased SIRT3 expression (24). In contrast, 12 weeks of resistance training did not increase SIRT3 levels in adolescents (25). Similarly, 10 weeks of resistance training failed to increase SIRT3 levels in skeletal muscle of middle-aged individuals (26). Overall, these studies suggest that exercise-induced changes in SIRT3 are protocol-dependent, and that resistance training can ameliorate the age-related suppression of SIRT3 but does not improve SIRT3 levels in adolescents and middle-aged individuals. These results for endurance training are consistent with the results of the present study; however, the results for resistance training are inconsistent. Thus, different protocols may account for the inconsistency of the results.

The physiological mechanisms of exercise-induced increases in sirtuin activity are not fully understood, but may be mediated by exercise-induced changes in the NAD+/NADH- or AMP/ATP ratios. This explanation is supported by the results of a study that reported that 10 weeks of resistance training resulted in increased muscle NAD+ levels and higher sirtuin activity in untrained, middle-aged participants (26). Comparing the results of the studies, it was found that the enzymatic capacity was higher in younger participants than in older participants (27). Overall, the analyses showed that SIRT3 activity increased in response to exercise intervention and that this increase could potentially be further enhanced by dietary modifications (27). The results of this study were inconsistent with the results of the present study for both endurance and resistance training. It is possible that inadequate sumac dosages or training regimens contributed to these inconsistent results.

In another study, it was found that the amount of resveratrol supplementation at different doses caused different changes in the SIRT3 variable (28). These results were not consistent with the results of the present study, and considering the results of the above study, it can also be hypothesized that different doses of sumac supplementation may lead to different changes in the amount of SIR3 and SIRT4 variables, and the absence of significance of changes in this variable may be due to the insufficient amount of supplement intake. In another study, the effects of rosemary extract and physical activity on hippocampal function and antioxidant capacity in aged rats were compared, and the results showed that rosemary extract can increase working memory and antioxidant activity in aged rats (29). Similarly, cocoa flavanol supplementation increases NAD metabolism and stimulates sirtuin metabolism and improves mitochondrial function (30). Furthermore, the results of a study showed that aerobic exercise along with saffron consumption increased mitochondrial biogenesis in rats (31), which is consistent with the results of the present study.

Recent studies have shown that many metabolic diseases, including obesity, diabetes, hypercholesterolemia, and cardiovascular disease, are risk factors for cognitive impairment and increase the risk of AD. Considering that AMPK is a key regulator of cellular and whole-body energy balance, including glucose and lipid metabolism and mitochondrial biogenesis, it is tempting to link AMPK to metabolic

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disorders and AD. Results show that moderate-intensity cycling exercise (90 min) in humans leads to increased AMPK activity and phosphorylation in muscle biopsies (32). Treadmill running in rats also leads to increased AMPK phosphorylation in all glycolytic and oxidative muscles used (32). These results are not consistent with the results of the present study, which may be due to different training programs. It is unclear whether these pathologies are caused by the same mechanisms (such as a deficiency in AMPK activation) or whether they are caused by the development of cerebrovascular diseases. However, there are many similar pathological features associated with AMPK abnormalities that are present in both diseases, including mitochondrial dysfunction, which is an important factor in AD and metabolic syndrome (16).

In another study, results showed that acute and chronic resistance training can increase AMPK levels, which was inconsistent with the results of the present study. Specifically, high-intensity training showed greater AMPK activity, while AMPK activity remained unchanged in the low-intensity group, indicating that AMPK activity is positively correlated with exercise intensity. Furthermore, it has been reported that AMPK increases by 75% immediately after a period of resistance training, and AMPK activity is closely related to exercise intensity, and the degree of activation dependents on training load (33). The reason for these conflicting results could be due to the difference in exercise intensity in this study and the present study.

Finally, our results indicated that endurance and resistance training can improve the variables studied in this study and can probably be used to reduce complications or slow down the progression of AD. Considering the results obtained in the present study, it seems necessary to conduct similar studies using different doses of sumac supplements to achieve the appropriate ratio of supplements. On the other hand, adopting a healthy lifestyle using appropriate diets helps prevent and treat metabolic syndrome. To investigate the potential role of sirtuins, it is also recommended to conduct a study in different age groups and in patients with and without metabolic disorders.

Conflict of interest: There were no conflicts of interest.

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