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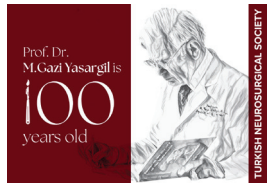

Syringic Acid Reduces Subarachnoid Hemorrhage–Induced Oxidative Damage in Rats

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ABSTRACT

AIM: To investigate the neuroprotective effects of various amounts of syringic acid (SA) on cerebral damage resulting from experimentally induced subarachnoid hemorrhage (SAH) in rats, utilizing both histological and biochemical analyses.

MATERIAL and METHODS: In total, 40 male Wistar albino rats were randomly and equally assigned to four groups: Control, SAH, SAH + 50 mg/kg/day SA (po), and SAH + 250 mg/kg/day SA (po). The rats in the SAH, SAH + 50 mg/kg/day SA, and SAH + 250 mg/kg/day SA groups were induced with SAH by administering 0.15 mL of autologous blood, collected from each rat's heart, into the subarachnoid space through the foramen magnum. On day 10th, the rats were sacrificed, and their blood and brain tissues were collected for biochemical, and histological analyses.

RESULTS: Glutathione peroxidase levels were considerably elevated in the SAH + 250 mg/kg/day SA group compared to both the control and SAH groups. Although not statistically significant, IL-6 levels were lower in the SAH + 250 mg/kg/day SA group compared with those in the control group. In the SAH + 250 mg/kg/day SA group, the histological and cellular damages in the cortical brain tissue reduced significantly.

CONCLUSION: SA (250 mg/kg/day) ameliorated the oxidative and histopathological changes in blood profile and cerebral tissue of rats when exposed to experimentally induced SAH. Thus, SA can reduce secondary cerebral damage in an SAH-induced rat model.

KEYWORDS: Syringic acid, subarachnoid hemorrhage, oxidative stress, rat

ABBREVIATIONS: CAT: Catalase, **FORs:** Free oxygen radicals, **Gpx:** Glutathione peroxidase, **GSH:** Glutathione, **IL:** Interleukin, **MDA:** Malondialdehyde, **SAH:** Subarachnoid hemorrhage, **SA:** Syringic acid, **SOD:** Superoxide dismutase, **TNF-α:** Tumor necrosis factor alpha

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a severe form of hemorrhagic stroke with high morbidity and mortality rates (24). Current treatment guidelines for SAH still do not provide a definitive solution (7). In patients with SAH, cerebral damage often occurs due to delayed complications, most commonly associated with cerebral ischemia caused by hemorrhage (1). During ischemia, impaired glucose and oxygen supply leads to calcium influx, which in turn triggers apoptosis by activating mitochondrial permeability transition (30).

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The free oxygen radicals (FORs) produced by mitochondria initiate apoptotic pathways (9). The increase in neuronal apoptosis induced by free oxygen radicals (FORs) underlies the pathogenesis of chronic neurodegeneration and acute central nervous system trauma (26). Cellular defensive potential functions as a critical protective system against oxidative damage triggered by FORs (15). Malondialdehyde (MDA), a byproduct of lipid peroxidation, is a key marker of oxidative damage (32). Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx) help protect tissues against FORs and lipid peroxidation (5). Previous studies have shown elevated levels of reactive oxygen species (ROS) and MDA, alongside significantly reduced in antioxidant activity, in a rat model of cerebral ischemia (21,22). Impairment of the protective mechanisms against oxidation induces oxidative harm to neural lipids, proteins, and genetic material, eventually culminating in nerve cell death (33). Proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) play a central role in inflammation (10). These small-scale molecular compounds are secreted by cellular entities when triggered by pro-inflammatory signals (14). Evaluating levels of MDA, CAT, GSH, GPx, SOD, TNF-α, IL-1β, and IL-6 is therefore essential to assess SAH-induced oxidative and inflammatory damage (19).

In recent years, there has been a growing focus on reducing secondary cerebral damage, with several pharmacological agents such as curcumin and nitric oxide under investigation (11,20). Phenolic acid derivatives are of particular interest owing to their ability to scavenge free radicals and suppress oxidative stress (6). Syringic acid (SA), a phenolic acid derivative with no observed toxicity up to 1,000 mg/kg/day (22,23), has antioxidant, antiproliferative (16), antiendotoxic (34), and anticarcinogenic properties (10). It has been shown to reduce inflammation and oxidative stress in various neurodegenerative disease models (29). However, no study has yet evaluated the effect of SA on SAH-induced brain damage. Therefore, this study aims to biochemically and histologically explore the neuroprotective effects of different SA doses on oxidative damage in rats after experimentally inducing SAH. This is the first study to investigate the effect of SA in SAH-induced oxidative brain damage.

MATERIAL and METHODS

Ethics Statement

The research was executed in alignment with the protocols for the handling and welfare of lab animals established by the National Institutes of Health. The investigation received sanction from our institution's Animal Research Ethics Board. (No: 2023 HADYEK-13/51879863-41; Dated: August 17, 2023).

Animals

Forty male Wistar albino rats (aged 8–10 weeks; weighing 230–250 g) were procured from the Laboratory Animal Research Center of Tokat Gaziosmanpaşa University. They were fed standard commercial pellet feed and allowed ad libitum access to water. The rats were housed at a temperature of 22°C ± 1°C, with a relative humidity of 55% ± 5%, under a 12-h light/dark cycle.

Procedure

Overall, 40 male Wistar albino rats were randomly and equally assigned to the following four groups: Group 1, Control; Group 2, SAH; Group 3, SAH + 50 mg/kg/day SA; and Group 4, SAH + 250 mg/kg/day SA. After the rats were anesthetized using xylazine/ ketamine, SAH was induced in the rats in Groups 2, 3, and 4 by injecting 0.15 cc of autologous blood, collected from each rat's heart, into the subarachnoid space via the foramen magnum (18). Following the protocol, the rats were tracked throughout the investigation. A total of 10 rats died during the monitoring period (Group 2, n = 4; Group 3, n = 3; and Group 4, n = 3). In Groups 3 and 4, SA was administered orally once daily via a nasogastric tube. To control for handling stress, rats in the other groups received physiological saline via the same method. The rats were sacrificed on the 10th day after the procedure for biochemical analysis and histopathological evaluations.

Biochemical Analysis

Immunological methods were employed to evaluate oxidative stress markers within the rodent blood plasma. Reduced GSH levels were assessed using the competitive (inhibition) enzyme immunoassay (EIA) technique. It was measured at 450 nm and expressed in ng/mL. The CAT, GPx, and SOD levels (ng/mL) were determined using the sandwich EIA technique at 450 nm. The level of MDA (pg/mL), an end-product of the peroxidation of polyunsaturated fatty acids, was measured at 450 nm using the competitive (inhibition) EIA technique. The level of IL-1β (ng/mL), which is crucial in regulating the immune response and inflammation, was measured using the sandwich EIA. The level of IL-6 (pg/mL) was measured at 450 nm using the sandwich EIA. Similarly, the level of TNF-α (ng/mL), another key proinflammatory cytokine, was assessed using a double-antibody sandwich enzyme linked immunosorbent assay.

Histological Procedures

Hematoxylin–eosin staining

The tissue sections from the brain, including the cerebellum, were fixed in formalin and embedded in paraffin blocks. The sections were deparaffinized, rehydrated, and immersed in hematoxylin solution. After rinsing the hematoxylin-stained sections under running water, they were immersed in acid alcohol, rinsed with distilled water, and immersed in eosin solution. Subsequently, the sections were washed with distilled water and processed through a series of alcohol solutions (80%, 90%, 95%, and 99%) followed by xylene. Finally, coverslips were applied to the sections.

Histopathological analysis

Hematoxylin–eosin-stained slices of brain and cerebellum samples were examined via light microscopy (ECLIPSE TS-200; Nikon, Tokyo, Japan). The severity of injury in the brain and cerebellum specimens was evaluated semi-quantitatively, graded as normal, mild, moderate, or severe (Table I) (18). All

microscopic tissue examinations were conducted by a skilled histopathologist (FG) utilizing a blinded coding protocol.

Statistical Analysis

The general characteristics of the groups were descriptively analyzed. Continuous variables are expressed as means with standard deviations. One-way analysis of variance was used to compare the means of quantitative variables between the study groups. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SPSS (version 22.0; Chicago, IL, USA).

RESULTS

Biochemical Results

The levels of GSH, GPX, IL-1 β, IL6, CAT, MDA, SOD, and TNF-α in the four study groups are presented in Table II.

Histopathological Results

In the control group, neurons in the cortical brain tissue exhibited a typical histological appearance (Figure 1A). In Group 2, severe structural degeneration were observed, including intraparenchymal hemorrhage, shrinkage of cerebral cortex neurons, and densely darkly stained heterochromatic pyknotic nuclei. In Group 3, these damages had decreased to some extent. In Group 4, histological and cellular damage in the cortical brain tissue was significantly decreased (Figure 1B–D).

In the control group, the Purkinje cells and granular layer of the cerebellar cortex showed a normal histological structure (Figure 2A). In Group 2, the Purkinje cells were deformed, with shrunken cytoplasm and pyknotic nuclei densely stained with heterochromatin. Furthermore, there was a reduction in Purkinje cells, thinning of the granular layer, and pronounced congestion and hemorrhage in the molecular layer. Group 3 showed slight improvement, while Group 4 demonstrated a significant reduction in degenerative tissue and cellular damage (Figure 2B–D).

Table I: Cerebral and Cerebellar Tissue Damage Scoring Criteria (18)

Grades	Criteria
0	Normal
1	Mild
2	Moderate
3	Severe

DISCUSSION

SA has been used effectively in several neurodegenerative diseases (12). In a study conducted on rats using an experimental ischemia-reperfusion model, SA administered at four doses significantly reduced oxidative stress by increasing the antioxidant enzyme level of cell damage in hippocampal neuronal cells and had strong neuroprotective effects (4). In another rat study, SA (25 mg/kg/day) improved neuronal damage via its antioxidant and antiapoptotic activity in a study evaluating neurotoxicity induced by the insecticide deltamethrin (25). In this study, we investigated the antioxidant effects of SA at different doses for treating SAH-induced brain damage. Our findings indicate that in a SAH rat model, daily dose of 250 mg/kg SA significantly increased GPx levels, suggesting enhanced antioxidant activity and a reduction in oxidative damage. Furthermore, its therapeutic effect on the histopathological changes in the brain tissue were also observed.

Previous studies reported model-related mortality rates of up to 47% in experimental SAH models (31). In our study, considering that model-related mortality may occur at specified rates, the study was started with 10 rats per group. A total of 10 rats died in all groups during the experimental period. However, power analysis conducted before the experiment

Table II: Blood Oxidant, Antioxidant, and Proinflammatory Cytokines Values

Variables	Overall	Groups				p-value
		Control	SAH	SAH + SA-50	SAH + SA-250	
GSH	99.87 ± 29.8	98.94 ± 23.72	114.77 ± 8.78	105.34 ± 21.42	85.72 ± 48.35	0.490
GPX	36.47 ± 6.01	31.64 ± 3.46^{a}	33.07 ± 3.65^{ab}	39.36 ± 3.07^{bc}	41.47 ± 6.74^{c}	**0.003**
IL-1 β	26.65 ± 0.16	26.7 ± 0.15	26.55 ± 0.05	26.61 ± 0.18	26.69 ± 0.2	0.400
IL6	22.59 ± 11.93	22.15 ± 13.86	14.8 ± 10.55	29.25 ± 13.07	21.7 ± 6.73	0.320
CAT	4.94 ± 0.96	5.05 ± 0.92	5.29 ± 0.74	5.05 ± 1.44	4.44 ± 0.45	0.531
MDA	125.34 ± 53.55	151.49 ± 55.73	96.79 ± 15.58	104.62 ± 68.22	130.24 ± 41.86	0.272
SOD	0.36 ± 0.08	0.39 ± 0.13	0.38 ± 0.07	0.35 ± 0.05	0.31 ± 0.02	0.407
TNF-α	106.96 ± 14.96	98.4 ± 12.97	109.47 ± 17.99	113.73 ± 19.33	109.93 ± 6.16	0.248

SAH: *Subarachnoid hemorrhage;* ***SA:*** *Syringic acid;* ***GSH:*** *Glutathione;* ***GPx:*** *Glutathione peroxidase;* ***IL-1β:*** *İnterleukin-1β;* ***IL-6:*** *İnterleukin-6;* ***CAT:*** *Catalase;* ***MDA:*** *Malondialdehyde;* ***SOD:*** *Superoxide dismutase;* ***TNF-α:*** *Tumor necrosis factor alpha.*
One-way analysis of variance was used. a, b, and c, means with common letters in the same row did not differ significantly.

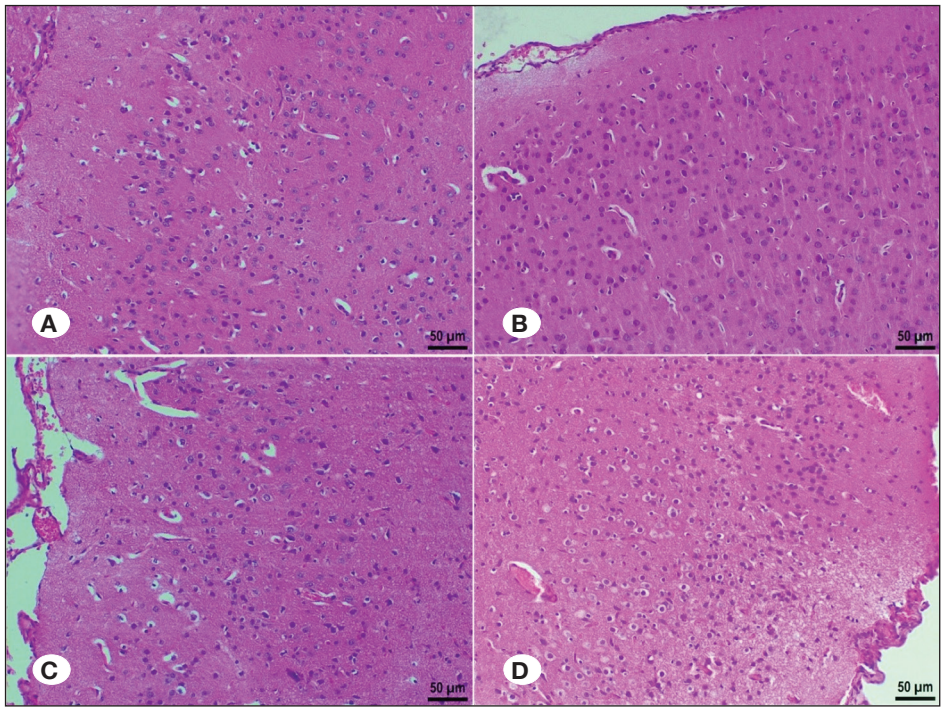

Figure 1: Representative microscopic images of cerebral tissue from the study groups. **A (control):** Normal histological appearance. **B (SA-250):** Marked reduction in histological and cellular damage in the cerebral tissue. **C (SA-50):** Mild reduction in the histological and cellular damage. **D (SAH):** Congestion and hemorrhagic areas as well as neuronal degenerative damage in the cortical tissue (hematoxylin–eosin staining; scale bar: 50 µm).

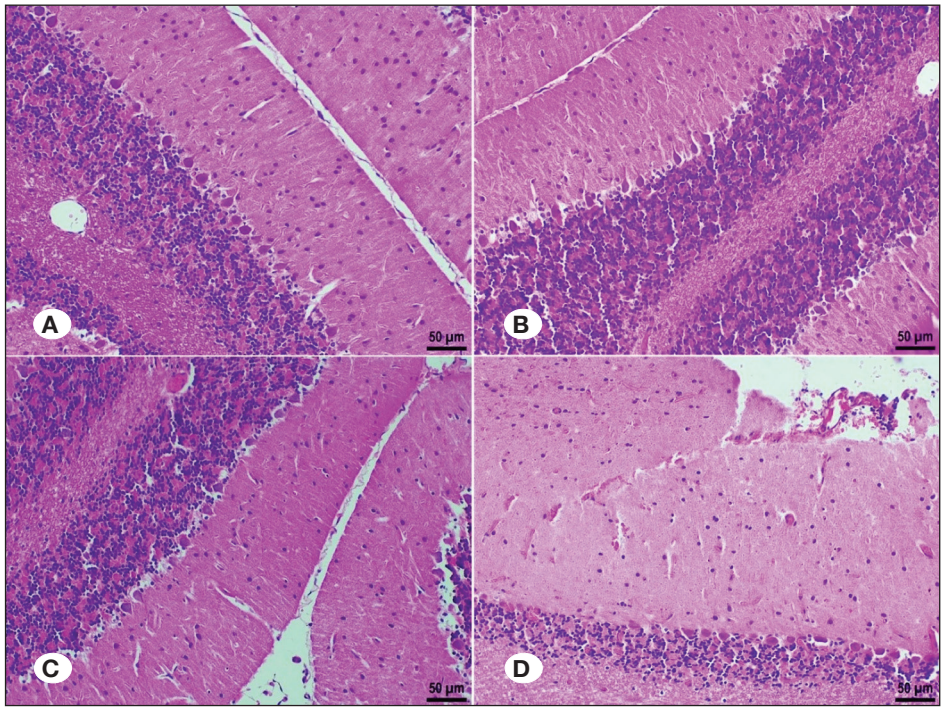

Figure 2: Representative microscopic images of cerebellar tissues from the study groups. **A (control group):** Normal histological appearance. **B (SA-250):** Pronounced decrease in the damage, resulting in an appearance similar to normal cerebellar tissue. **C (SA-50):** Moderate tissue and cellular damage. **D (SAH):** Purkinje cells with shrunken cytoplasm, dense heterochromatin-stained pyknotic nuclei, and reduced granular cell layer. Furthermore, the molecular layer exhibits intense tissue damage characterized by inflammatory cells, congestion, and hemorrhagic areas (hematoxylin–eosin staining; scale bar: 50 µm).

Table III: Molecules Used in Subarachnoid Hemorrhage Studies in Rats

Molecule	Article
Nimodipine, (2)	Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, Van Effenterre R. (2004). Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. American Journal of Neuroradiology, 25(6), 1067-1076.
Curcumin, (19)	Kuo CP, Lu CH, Wen LL, Cherng CH, Wong CS, Borel CO, Ju DT, Chen CM, Wu CT. (2011). Neuroprotective effect of curcumin in an experimental rat model of subarachnoid hemorrhage. Anesthesiology, 115(6), 1229-1238. https://doi.org/10.1097/aln.0b013e31823306f0
Secukinumab, (17)	Kiyak V, Gevrek F, Demir O, Katar M (2024). Secukinumab Ameliorates Oxidative Damage Induced by Subarachnoid Hemorrhage. World Neurosurgery, 190, e158-e164. https://doi.org/10.1016/j.wneu.2024.07.080

determined that a minimum of five rats per group were required for statistical significance. The number of rats that remained healthy in our study exceeded this number. Therefore, the observed mortality did not affect the statistical reliability of our results.

Numerous therapeutic agents have been used to reduce SAH-induced brain damage (Table III). In a study using an experimental SAH model in rats, Secukinumab significantly reduced oxidative stress and played a crucial role in the recovery of resulting brain damage (17). In another rat study, curcumin was reported to have antioxidant effects and reduced mortality in the SAH group (19). In a study on patients with SAH, intra-arterial administration of nimodipine reduced vasoconstriction, thereby decreasing brain damage secondary to SAH (2).

Antioxidant enzymes like, CAT, GSH, SOD, and GPx are vital for counteracting the effects of ROS in tissues. FORs interact with unsaturated fatty acids in cell membranes, triggering lipid peroxidation. Lipid peroxides decompose into secondary products like MDA (27,28). These products induce oxidative damage in DNA and other tissues, which are directly or indirectly responsible for cell death in brain tissue (28). FORs released following SAH and subsequent brain damage reduce the levels of various endogenous antioxidant enzymes, such as SOD, GSH, GPx and CAT, altering their activities (27). In one study, stanniocalcin-1 decreased oxidative stress and reduced the associated brain dysfunction (3). In another study, quercetin increased SOD and GPx levels and significantly decreased MDA levels in an experimental SAH model (8). These studies demonstrated that oxidative stress is involved in the pathogenesis of secondary brain damage, and agents that help increase the effectiveness of antioxidant systems may decrease brain damage by reducing oxidative stress. In our study, the levels of SOD, GSH, CAT, GPx, MDA, IL-6, TNF-α, and IL-1β were analyzed to identify secondary brain damage after SAH. Our results revealed that SAH induced changes in the levels of antioxidant enzymes—such as GPx, GSH, CAT, and SOD —and markers of oxidative stress—such as MDA. We found that the GPx level was significantly higher in the SAH group receiving 250 mg/kg/day SA than in the control and SAH groups (Table I). These results suggest that SA may help decrease FORs by enhancing the levels of the antioxidant enzyme GPx. This may contribute to the alleviation of cerebral damage by hindering lipid peroxidation.

IL-6, IL-1β, and TNF-α are proinflammatory cytokines, and their blood levels increase during inflammation. This increase may induce neurotoxic effects, leading to brain tissue damage (33). Elevated IL-6 levels are also associated with delayed cerebral ischemia (9). In our study, although not statistically significant, we observed a reduction in IL-6 levels in the SAH group receiving 250 mg/kg/day SA compared with that in the control group. This indicates that SA may suppress inflammation and contribute to reducing potential brain damage.

SAH-induced microscopic tissue injury in neural tissue stems from a disruption in the balance between oxidative stress and antioxidant defenses. Experimental studies using cysteamine and sodium orthovanadate have shown that reducing SAH and oxidative stress, which are responsible for subsequent damage, also helps protect against histopathological changes (13,35). In our study, histological and cellular damage decreased slightly in the SAH group treated with 50 mg/kg/day of SA (Figure 1). However, in the SAH group treated with 250 mg/kg/day of SA, histological and cellular damage in the cortex had remarkably reduced. Marked programmed cell death is observed in the brain neuronal cells of rats due to SAH and its accompanying alterations (15). In a study that examined the effects of SA in an ischemic rat model, oxidative stress and neuronal degeneration decreased after SA administration (11). In our study, the SAH group treated with 50 mg/kg/day SA exhibited moderate tissue and cellular damage. However, in the SAH group treated with 250 mg/kg/day SA, the cerebellar tissue appeared almost normal. These results indicate that SA reduces the histological damage to brain tissue caused by oxidative stress. Therefore, a daily dose of 250 mg/kg SA plays a crucial role in minimizing SAH-induced brain damage and preventing histopathological alterations in brain tissue.

CONCLUSION

SA treatment (250 mg/kg/day) effectively reduced oxidative stress and neuronal degeneration in a rat experimental model of SAH. Our biochemical and histopathological findings suggest that SA is an alternative treatment modality for SAH due to its antioxidant and neuroprotective properties. There are certain limitations in our study. Although our results suggest that

SA has neuroprotective benefits in mitigating brain damage induced by SAH, additional pharmacokinetic studies and investigations into the safe-dose range are required before it can be incorporated into human treatment protocols. Another limitation is the death of 10 rats during the study.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: VK, OD
Data collection: FG, OD, MK
Analysis and interpretation of results: VK, OD, FG, OD, MK
Draft manuscript preparation: VK
Critical revision of the article: VK, OD
Other (study supervision, fundings, materials, etc...): VK
All authors (VK, OD, FG, OD, MK) reviewed the results and approved the final version of the manuscript.

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