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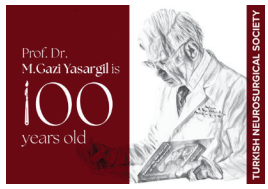

Investigation of the Effects of Quercetin on Early Brain Injury and Vasospasm in an Experimental Model of Subarachnoid Hemorrhage

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ABSTRACT

AIM: To investigate the therapeutic efficacy of quercetin in early brain injury (EBI) and vasospasm resulting from experimental subarachnoid hemorrhage (SAH).

MATERIAL and METHODS: The rats were assigned into five groups, as follows; Group A: rats did not undergo SAH induction, Group B: rats underwent SAH induction, but received no treatment, Group C: rats underwent SAH induction and received dimethyl sulfoxide (DMSO) intraperitoneally, Group D: rats underwent SAH induction and followed by the intraperitoneal administration of 10 mg quercetin, Group E: rats underwent SAH induction, followed by the intraperitoneal administration of 50 mg quercetin. After the procedure, each group of rats received DMSO, 10 mg/kg quercetin, or 50 mg/kg quercetin intraperitoneally at 30 minutes, 12 hours, and 24 hours, according to their respective categories. The oxidative stress index (OSI) was biochemically measured using the total oxidant status and total antioxidant status. The serum caspase-3, glutathione peroxidase-1 (GPX), and malondialdehyde (MDA) levels were measured.

RESULTS: Brain injury and vasospasm after SAH led to a decrease in the serum GPX levels and an increase in the caspase-3, MDA, and OSI levels. Vasospasm induced an increase in the wall thickness and a narrowing of the lumen diameter in the basilar artery. Treatment with quercetin increased the GPX level and decreased the caspase-3 and MDA levels. Treatment with quercetin reduced the wall thickness and increased the lumen diameter of the basilar artery.

CONCLUSION: Quercetin may be a novel, effective therapeutic option for the treatment of cerebral vasospasm and brain injury by reducing apoptosis, oxidative damage, vessel wall thickness, and vasoconstriction.

KEYWORDS: Early brain injury, Oxidative damage, Quercetin, SAH, Cerebral vasospasm

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INTRODUCTION

Subarachnoid hemorrhage (SAH) is a neurological condition characterized by the extravasation of blood into the subarachnoid space and is associated with significant mortality and morbidity. Vasospasm, which occurs after SAH, is a major pathological condition that adversely affects mortality and morbidity. Early brain injury (EBI) is the leading cause of death during the first 72 hours after SAH, and should therefore be investigated for combating mortality and morbidity after SAH. Some alterations that lead to vasospasm and EBI include the disruption of cerebral perfusion, activation of the inflammatory pathways, disruption of the blood–brain barrier (BBB), oxidative stress, and the activation of apoptosis (6,11).

Quercetin is a bioflavonoid abundant in plant foods that has been widely examined for its protective effects on human health in recent years. Quercetin, or 3,3′,3′,4′,4′,5,7-pentahydroxyflavone, is a more widely available dietary flavonol compared with other phytochemicals.

It has been demonstrated previously that quercetin possesses multiple antioxidant, anticarcinogenic, neuroprotective, anti-inflammatory, cardioprotective, antiallergic, and antiosteoporotic effects (4,7,12,14,15,18). Accordingly, in the present study, we aim to determine the therapeutic properties of quercetin against vasopasm, and EBI resulting from SAH.

MATERIAL and METHODS

Animals and the Experimental Design

This study received project support (No. 2021/124) from the Health Sciences University Scientific Research Project. This study was approved by the Ege University Animal Experiments Local Ethics Committee (No. 2021-016) and was conducted at the Ege University Laboratory Animal Research and Application Center.

The study was conducted with 40 healthy adult male and female Wistar Albino rats, weighing 250–400 g and raised at the Ege University Laboratory Animals Application and Research Center; these rats had not been used in any previous experiments. The animals were categorized into five groups of eightrats each. The rats were assigned identification numbers and divided into groups based on block randomization. The Group A rats did not undergo SAH induction. In the intervention groups, 0.1-mL cerebrospinal fluid (CSF) was extracted and 0.1-mL of autologous (intracardiac) blood was injected into the cisterna magna. The Group B rats underwent SAH induction but received no treatment. The Group C rats underwent SAH induction and received dimethyl sulfoxide (DMSO), the drug solvent, intraperitoneally. The Group D rats underwent SAH induction and received 10 mg/kg quercetin in DMSO intraperitoneally. The Group E rats underwent SAH induction and received 50 mg/kg quercetin in DMSO intraperitoneally (Table I). During the experiment, the rats were housed at 25°C in a 12-h light/dark cycle. Care was taken to avoid any conditions that would induce stress in the rats. During the study, four rats were lost in Group C. There were no losses in the other groups. The study was completed with 36 rats; two of the losses occurred during SAH induction and two occurred during follow-up before 48 hours had elapsed. Some of the rats were lost due to surgical complications during and after the procedure. All rats that died in the experiment were in the DMSO group, which may indicate the high neurotoxicity of the solvent DMSO. Although DMSO is also present as a solvent in the quercetin groups, we hypothesized that quercetin could antagonize the neurotoxicity of DMSO. For further research, it is necessary to increase the number of rats in the experiment. The rats that died were excluded from the study considering the possibility of them not displaying cellular changes expected in EBI and of dying from other causes (e.g., intracardiac blood sampling, complications of surgery, and complications of anesthesia).

Experimental Rat Model of Subarachnoid Hemorrhage

The rats assigned for SAH induction were sedated with intraperitoneal ketamine (90 mg/kg IM - additional dose 10 mg/kg) + xylazine (10 mg/kg - additional dose 5 mg/kg). The efficacy of anesthesia was confirmed by delivering painful stimuli. Before conductingthe surgical procedure, the rats received amoxicillin as a prophylactic antibiotic and the analgesic meloxicam.

After anesthesia, the rats were placed in an appropriate position for surgery. Autologous cardiac blood was used as a whole blood sample (Figure 1A). Then, 0.3 cc of intracardiac blood was collected percutaneously using a 24-G insulin syringe. The surgical site was sterilized with povidone-iodine, and the head was flexed at 30 degrees, after which an incision was made on the skin between the inion and C1. The splenius muscles were retracted, and the atlantooccipital membrane was exposed (Figure 1B).

A 26-G cannula was inserted into the cisterna magna and advanced by 1–2 mm. Then, 0.1-mLof CSF was extracted and

Table I: Experimental Groups and Their Characteristics

Group	Number of Experimentals	Category
A	8	Control Group
B	8	Subarachnoid Hemorrhage (SAH) Group (SAH Group)
C	4	SAH + Dimethyl Sulfoxide Group (DMSO Group)
D	8	SAH + 10 mg/kg Quercetin Group
E	8	SAH + 50 mg/kg Quercetin Group

0.1-mL autologous blood was injected into the cisterna magna. There after, the wound was closed by using an intradermal suture and local antibiotic, and tetracycline was applied to the incision site as the active ingredient.

After the procedure, each rat received either DMSO, 10 mg/kg quercetin, or 50 mg/kg quercetin intraperitoneally at 30 min, 12 h, and 24 h, depending on the respective category. The treated rats were monitored for 48 h for neurologic deficits and general conditions. At 48 h, 4 cc of blood was collected before decapitation from each rat that was not excluded from the experiment and the samples were stored under optimal conditions. The rats were then decapitatedin accordance with the standard procedures, and the brain was resected in full and transferred into a 10% neutral-buffered formalin solution (10% formaldehyde, 4g/L NaH_2P0_4, and 6g/L Na_2HP0_4) for fixation before histological examination (Figures 2A, B).

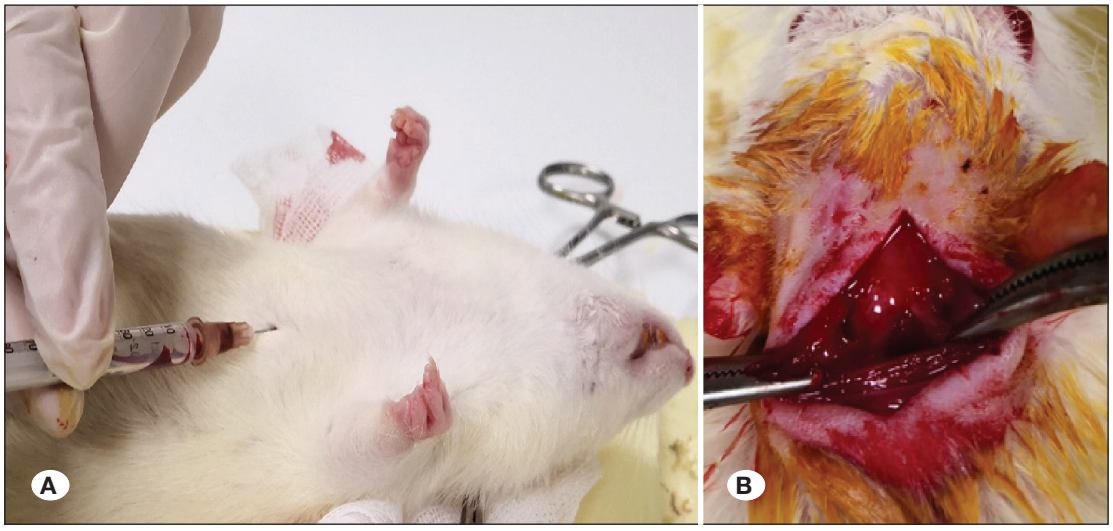

Figure 1:
A) The technique of collecting intracardiac blood from rats;
B) atlantooccipital membrane exposed after incision.

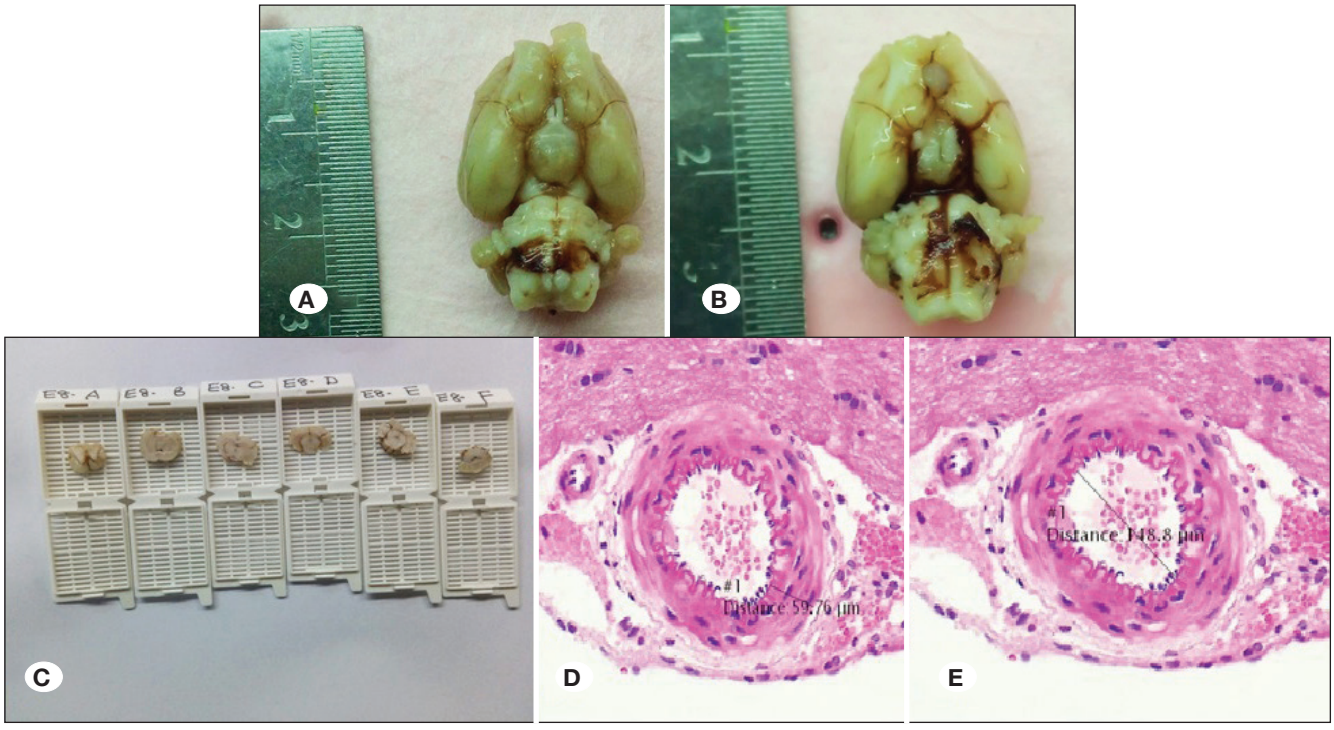

Figure 2: A) A macroscopic image of a rat brain from the control group; **B)** macroscopic image of a rat brain after subarachnoid hemorrhage (SAH) induction. **C)** Preparation of tissue samples for microscopic assessment; **D)** microscopic measurement of the wall thickness of the basilar artery [Hematoxylin and Eosin (H&E, x400)]; **E)** microscopic measurement of the lumen diameter of the basilar artery (H&E, x400).

The tissue samples were processed for assessment under light microscopy. The samples were fixed in 10% formalin in phosphate buffer overnight, processed using routine histologicaltechniques, and embedded in paraffin blocks. The paraffin blocks were placed in a rotary microtome (Leica RM2245, Germany) and divided into 5-µm sections (Figure 2C). The sections were deparaffinized; hydrated; stained with hematoxylin and eosin; evaluated at 10×, 20×, and 40× magnification; and photographed using an Olympus microscope (BX50, Olympus, Japan). The lumen diameter and wall thickness of the basilar artery were then measured and recorded (in µm) (Figures 2D, E).

To assess apoptosis, apoptotic cells were counted in ten different 40× magnification regions and recorded in terms of their ratio to the total cell count. Apoptotic bodies (a morphological feature of apoptosis), nuclear fragmentation, and pyknotic nuclei were evaluated (Figure 3).

Blood samples were allowed to clot for 30 min and then centrifuged at 3000 rpm for 10 min at room temperature. Some of the serum samples obtained were used for TAS and TOS analyses. The results were expressed in mmol Trolox equivalent/L for TAS and µmol H_20_2 equivalent/L for TOS. The OSI values, which were used as indicators of the oxidative load, were calculated based on the following formula: 100 ×(TOS [µmol H_20_2 equivalent/L] / TAS [mmol Trolox equivalent/L]).

Serum rat caspase-3 (Casp3) and serum rat glutathione (GSH) peroxidase-1 (GPX1) levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Wuhan Fine BiotechCo., Ltd., China). The serum rat MDA levels were also measured by using an ELISA kit (Bioassay Technology Laboratory Jiaxing Korain Biotech Co., Ltd., China). The results were expressed in ng/mL for rat Casp3, pg/mL for rat GPX, and nmol/mL for rat MDA.

Statistical Analysis

Statistical analyses were performed usingthe SPSS software v. 22.0 (IBM, NY, USA). Afterprocessing the data with descriptive statistics, continuous variables were examined for normality of distribution using the Shapiro–Wilk and Kolmogorov–Smirnov tests. As the number of animals in the groups did not meet the requirements for the parametric tests, nonparametric tests were applied instead. Continuous parameters were compared between the groups using the Kruskall–Wallis test. The parameters with statistical differences were further processed using post-hoc analyses. The results were presented as medians (min–max). In all tests, statistical significance was set at $p<0.05$.

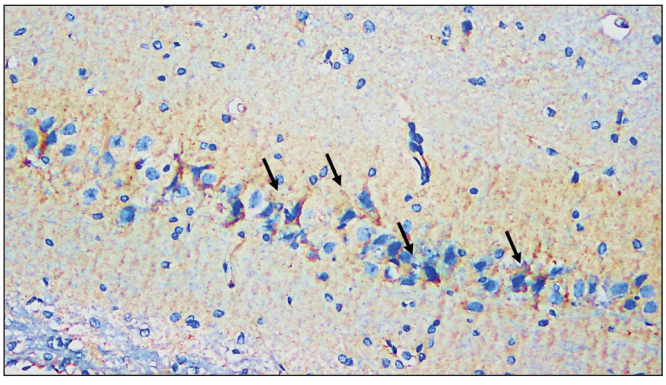

Figure 3: Cells immunoreactive for Caspase (arrow) x200 magnification.

RESULTS

The wall thickness of the basilar artery was significantly increased in Group B (77.6 µm [66.5–88.8µm]) compared to that in Group A (62.4 µm [49.5–69.6 µm]) (p=0.016) and significantly decreased in Group E (63.7 µm [50.0–73.6 µm]) when compared to that in Group B (p=0.049) (Table II).

The groups were compared in terms of the arterial lumen diameter, and its mean value was 250.8 µm in the control group. In Group B, the arterial lumen diameter was 175.8 µm. The difference in these values indicated a statistically significant narrowing in the arterial lumen diameter. The mean arterial lumen diameter was 212.6 µm in Group D and 223.9 µm in Group E. Both the groups treated with quercetin showed an increase in the mean arterial lumen diameter, albeit this increase was not statistically significant (p=0.071).

Degenerating neurons were significantly higher in Groups B (p<0.001), C (p=0.023), and D (p=0.031) than in Group A. The count of degenerating cells was not statistically significantly lower in Group D than in Group B, albeit it was statistically significantly lower in Group E (8.5 [4.0–85.0]) compared to that in Group B (135.0 [83.0–163.0]) (p=0.036).

In terms ofthe degenerating neuron/total neuron ratio, a statistically significant difference was noted among the control group (0.03 [0.0–0.11]) and the SAH group (0.75 [0.50–0.94]), the SAH+ DMSO group (1.0 [0.53–1.00]), and the SAH +10 mg quercetin group (0.70 [0.08–0.97]) (p=0.018, 0.001, and 0.028, respectively); all three groups showed significantly higher counts of degenerating neurons than the control group. The group treated with 50-mg quercetin was the closest to the control group in terms of the degenerating neuron/total neuron ratio.

The number of neurons stained for caspase-3 was significantly higher in Group B (4.5 [3.0–7.0]) than in Group A (0.0 [0.0–4.0]) (p=0.016) and significantly lower in Group E (1.5 [0.0–4.0]) compared to that in Group B (p<0.001); this finding demonstrated the treatmentefficacy. The number of neurons stained for caspase-3 was lower in Group D than inGroup B, albeit the difference was not statistically significant.

The number of neurons stained for GPX was significantly lower in Group B (2.0 [0.0–5.0]) than in Group A (8.5 [3.0–13.0]) (p=0.006) and significantly higher in Group E (7.5 [4.0–10.0]) than in Group B, which indicatedthe treatmentefficacy (p= 0,003). The number of neurons stained for GPX was higher in Group D than in Group B, albeit the difference was not statistically significant.

The groups were compared in terms ofthe laboratory parameters and found to have a statistically significant difference inthe serum MDA, GPX, caspase-3, and OSI levels. Post-hoc

Table II: Comparison of the Pathologic and Biochemical Characteristics in the Rat Groups

	Group A	Group B	Group C	Group D	Group E	p-value	Post hoc- analysis
Pathological features							
Arterial wall thickness median (min–max)	62.4 (49.5–69.6)	77.6 (66.5–88.8)	74.2 (66.1–85.0)	65.5 (56.4–78.0)	63.7 (50.0–73.6)	**0.007**	*Group A vs. Group B p=0.016 * Group E vs. Group B p=0.049
Arterial lumen diameter Median (min–max)	250.8 (164.4–302.1)	175.8 (132.6–268.2)	169.0 (146.7–191.8)	212.6 (172.2–169.3)	223.9 (148.8–383.7)	0.071	
Number of degenerating neurons median (min–max)	4.0 (0.0–16.0)	135.0 (83.0–163.0)	97.5 (71.0–170.0)	88.0 (8.0–129.0)	8.5 (4.0–85.0)	**<0.001**	*Group A vs. Group B p<0.001 * Group A vs. Group C p=0.023 * Group A vs. Group D p=0.031 *Group E vs. Group B p=0.036
Number of degenerating neurons/Total number of neurons Median (min–max)	0.03 (0.0–0.11)	0.75 (0.50–0.94)	1.0 (0.53–1.00)	0.70 (0.08–0.97)	0.11 (0.05–0.94)	**0.001**	*Group A vs. Group B p=0.018 * Group A vs. Group C p=0.001 * Group A vs. Group D p=0.028
Number of neurons stained for caspase median (min–max)	0.0 (0.0–4.0)	4.5 (3.0–7.0)	3.0 (1.0–4.0)	3.0 (1.0–4.0)	1.5 (0.0–4.0)	**0.001**	*Group A vs. Group B p<0.001 *Group E vs. Group B p=0.016
Number of neurons stained for GPX median (min–max)	8.5 (3.0–13.0)	2.0 (0.0–5.0)	1.5 (0.0–6.0)	4.5 (3.0–8.0)	7.5 (4.0–10.0)	**<0.001**	*Group A vs. Group B p=0.003 *Group E vs. Group B p=0.006
MDA (mmol/ml) median (min–max)	0.87 (0.84–0.91)	1.11 (0.92–1.32)	0.95 (0.90–1.04)	0.98 (0.72–1.08)	0.90 (0.85–0.93)	**0.002**	*Group A vs. Group B p=0.002 *Group E vs. Group B p=0.045
GPX (pg/ml) Median (min–max)	2241.8 (1824.8–3434.4)	1356.8 (1145.0–1500.3)	1538.8 (1173.0–1652.7)	1664.0 (1494.1–2149.3)	2106.0 (1884.5–2758.8)	**<0.001**	*Group A vs. Group B p=0.001 * Group A vs. Group C p=0.038 *Group E vs. Group B p=0.005
CASP3 (ng/ml) median (min–max)	0.35 (0.06–0.45)	1.15 (0.92–1.41)	1.03 (0.80–1.79)	0.86 (0.46–0.93)	0.47 (0.34–0.74)	**<0.001**	*Group A vs. Group B p<0.001 * Group A vs. Group C p=0.003 *Group E vs. Group B p=0.035
OSI median (min–max)	347.4 (217.8–894.9)	591.2 (509.3–728.6)	550.8 (436.4–575.7)	395.3 (349.3–1180.1)	515.0 (362.9–579.2)	**0.023**	*Group A vs. Group B p=0.015 * Group D vs. Group B p=0.048

analyses were performed to determine the groups that caused these statistical differences.

The serum MDA levels were significantly higher in Group B (1.11 mmol/mL [0.92–1.32 mmol/mL]) than in Group A (0.87 mmol/mL [0.84–0.91 mmol/mL]) (p=0.031) and statistically significantly lower in Group E (0.90 mmol/mL [0.85–0.93 mmol/mL]) than in Group B (p=0.014), demonstratingtreatmenteffi-cacy. The serum MDA levels were lower in Group D than in-Group B, albeit the difference was not statistically significant.

The serum GPX levels werestatistically significantly lower in Group B (1356.8 pg/mL [1145.0–1500.3 pg/mL]) (p=0.001) and in Group C (1538.8 pg/mL [1173.0–1652.7 pg/mL]) (p=0.038) than in Group A (2241.8 pg/mL [1824.8–3434.4 pg/mL]). Moreover, the serum GPX levels in Group E (2106.0 pg/mL [1884.5–2758.8 pg/mL]) were statistically significantly higher than those in Group B (p=0.036), demonstrating the the rapeutic efficacy of quercetin.

The serum caspase-3 levels were statistically significantly higher in Groups B (1.15 ng/mL [0.92–1.41 ng/mL]) (p<0.001) and C (1.03 ng/mL [0.80–1.79 ng/mL]) (p=0.003) than in Group A (0.35 ng/mL [0.06–0.45 ng/mL]). Group E showed statistically significantly lower serum caspase-3 levels (0.47 ng/mL [0.34–0.74 ng/mL]) than Group B (p=0.035). The serum caspase-3 levels in Group D (0.86 ng/mL [0.46–0.93 ng/mL]) were lower than those in Group B, although the difference was not statistically significant.

The serum OSI ratio was significantly higher in Group B (591.2 [509.3–728.6]) than in Group A (347.4 [217.8–894.9]) (p=0.015) and significantly lower in Group D (395.3 [349.3–1180.1]) than in Group B (p=0.048). There was no significant difference in the serum OSI values between Group E (515.0 [362.9–579.2]) and Group B.

DISCUSSION

SAH is an intracranial pathology associated with high mortality and morbidity. EBI is a major cause of death within the first 72 hours of developing SAH. EBI has been the target of research aiming to combat mortality and morbidity after developing SAH. Patients who develop SAH are at a risk of developing cerebral vasospasm and delayed cerebral is chemia. Vasospasm, which occurs after SAH, is a serious pathological condition that adversely affects mortality and morbidity. Vasospasm affects approximately 70% of patients 3–14 days after developing SAH (2,3,14).

Global ischemia resulting from SAH is followed by apoptosis in the hippocampus, BBB, and vascular system. Apoptosis occurs through several apoptotic pathways, such as the death receptor, caspase-dependent, caspase-independent, and mitochondrial pathways. Several studies suggest that p53 functions through the caspase-dependent pathway or mitochondrial pathway in SAH-induced apoptosis (14). Damage to the endothelial cells not only leads to BBB impairment but may also reduce the production of endothelium-dependent relaxing factors, which are presumed to locally exacerbate vasospasm. Clinically, it is probably a combination of all these factors that cause BBB impairment and vasospasm. The destruction of the BBB and subsequent edema are some of the leading causes of long-term cognitive dysfunction after SAH (16,17). Cerebral edema is an important component of EBI and is not a consequence of vasospasm, but rathera direct consequence of BBB impairment. The activation of inflammatory pathways, oxidative stress, alterations in electrolytes, and apoptosis may play an important role inthe later phases of EBI (5,14,11).

Quercetin is a bioflavonoid abundant in some plant foods and has been widely examined for its effectiveness in protecting human health in recent years. Quercetin possesses antioxidant, anticarcinogenic, neuroprotective, anti-inflammatory, cardioprotective, antiallergic, and antiosteoporotic properties (4,7,12,14,15,18). Quercetin prevents platelets, white blood cells, and endothelial cells, which are the main drivers of inflammation, from uniting. It exerts its anti-inflammatory effect by inhibiting the spontaneous apoptosis of neutrophils and reducing the sensitivity of neutrophils to inflammatory factors (16,17).

The findings of Kusaka et al. provided insight into the signaling pathways leading to EBI after SAH and reported that the formation of free oxygen radicals in the body triggers superoxided is mutase (SOD) to rapidly capture O_2 and convert it into H_2O_2, while GPX catalyzes the decomposition of H_2O_2 to nontoxic H_2O (9,10). This reaction requires GSH as the hydrogen source. Animal and *invitro* studies have revealed that quercetin induces GSH synthesis (9,10).The administration of quercetin in high doses influences the dynamic balance of GSH (under the influence of GPX), which leads to the conversion of H_2O_2 toH_2O, and GSH is converted to oxidized GSH disulfide. Quercetin regulates the GSH levels, thereby enhancing the antioxidant capacity of the body (10). The present study compared the study groups in terms of the number of neurons stained for GPX and the serum levels of GPX, revealing statistically significant differences in terms of quercetin treatment. This finding suggests that quercetin positively activates the antioxidant pathways.

MDA is one of the end products of polyunsaturated fatty acid peroxidation in cells. An increase in free radicals leads to MDA overproduction (13). MDA is known to be a marker of oxidative stress and antioxidant status in patients with cancer. Akkoyun et al. reported that quercetin treatment increases the levels of SOD and catalase and a decrease in MDA levels after lipopolysaccharide induction, suggesting that quercetin strengthens the antioxidant defense system (1,2). The present findings are consistent with those of previous studies in that the MDA levels were statistically significantly decreased in rats treated with quercetin.

Animal models of SAH studies conducted by Park et al. demonstrated the role of apoptosis in the formation of cerebral vasospasm (14). They also showed that caspase-3 inhibitors reduced oxyhemoglobin-induced apoptosis. Our study found that the number of neurons stained for caspase-3 as well asthe serum caspase-3 levels were significantly lower in rats treated with quercetin, suggesting that quercetin may suppress apoptosis, thereby preventing cerebral vasospasm.

Dong et al. investigated the efficacy of quercetin after SAH induction in rats (6). They assessed brain damage in rats immunohistochemically by comparingthe GPX, MDA, and caspase-3 levels. Notably, theanimals treated with 50-mg quercetin showed statistically significantly higher GPX activity and lower caspase-3 and MDA levels. This result is supported by our results, as we noted an increase in the GPX activity and a statistically significant decrease in the levels of caspase-3 and MDA in Groups D and E.

Gul et al. performed immunohistochemical analyses and found a significant decrease in the MDA levels in the group that received a high dose of quercetin (8). Microscopy analyses of the lumen diameter and wall thickness of the basilar artery found that high doses of quercetin were significantly beneficial. We compared Groups B and E and recorded a significant decrease in the wall thickness of the basilar artery with quercetin treatment. The lumen diameter of the artery was increased in Groups D and E, albeit this increase was not statistically significant.

Akkaya et al. examined the TAS, TOS, and OSI values in the brain tissues irrigated by the basilar artery in rats after SAH induction (1). The group that received intrathecal verapamil after SAH had higher TAS and lower TOS and OSI values compared to the control group. We then compared the groups in terms of OSI asan indicator of oxidative load and found it to be statistically significantly lower in Group D.

However, there are several limitations to this study. For instance, the number of rats used in the study was small and the study duration was short. Moreover, there exists no clear standard in the literature for the method of quercetin administration to rats and the choice of solvent.

CONCLUSION

Our study was based on the hypothesis that quercetin is a novel alternative treatment for brain damage and vasospasm resulting from SAH owing to its antioxidant, anti-inflammatory, and neuroprotective properties. Our results demonstrated the efficacy of quercetin against oxidative stress and apoptosis in SAH as assessed based on the biochemical, immunohistochemical, and microscopic parameters. Quercetin can be used to prevent early brain damage and vasospasm resulting from SAH. However, further experimental studies are warranted to translate the obtained data intopractice.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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: EK, HY, EA, CA, HBB, AT, ES, TK, GB, AA, OB, AY

Data collection: EK, HY

Analysis and interpretation of results: EK, HY, EA, CA, HBB, AT, ES, TK, GB, AA, OB, AY

Draft manuscript preparation: EK, HY

Critical revision of the article: EK, HY, EA, CA, HBB, AT, ES, TK, GB, AA, OB, AY

All authors (EK, HY, EA, CA, HBB, AT, ES, TK, GB, AA, OB, AY) reviewed the results and approved the final version of the manuscript.

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