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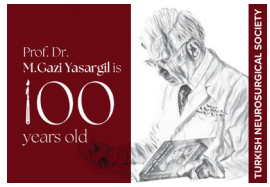

Investigation of the Protective and Therapeutic Effects of Ginger (Zingiber officinale) Extracts on Neuroinflammatory, Motor and Cognitive Impairments Caused by Mild Traumatic Brain Injury Model

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ABSTRACT

AIM: To examine the effects of phenolic compound-rich ginger extract on motor and cognitive functions as well as cytokine levels in the mild traumatic brain injury (mTBI) model.

MATERIAL and METHODS: The mTBI model was modeled employing the Marmarou method. The Ginger group rats were i.p. administered 50 mg/kg of ginger extract. The Ginger+traumatic brain injury (TBI) group rats were i.p. administered 50 mg/kg of ginger extract two days before the TBI was induced. The control and TBI+Ginger group rats were provided ginger extract (50 mg/kg i.p.) immediately after the TBI. Motor and cognitive behavioral experiments were performed. The cytokine levels were analyzed using the ELISA method.

RESULTS: While TBI caused a decline in motor and cognitive functions, significant enhancements of these functions were observed in the Ginger+TBI and TBI+Ginger groups because of the ginger treatment. While TBI induced an increased hippocampal cytokine level, significant decreases were detected in the Ginger+TBI and TBI+Ginger groups following ginger treatment.

CONCLUSION: The study findings revealed that phenolic compound-rich ginger extract may exert therapeutic effects on cytokine levels in the mTBI model.

KEYWORDS: Ginger, Cognitive function, Neuroprotective treatment, Therapeutic treatment, Mild traumatic brain injury

ABBREVIATIONS: NOR: Novel object recognition, **OF:** Open field, **TBI:** Traumatic brain injury

INTRODUCTION

Globally, traumatic brain injury (TBI) is a substantial cause of mortality and chronic disability that predominantly impacts adults (2). TBI often necessitates long-term treatment and care (8,10). The primary causes of TBI include traffic accidents, falls, occupational accidents, beatings, and gunshot wounds (30). Although it results in severe health problems, such as disability and death, effective diagnostic

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and treatment modalities are yet to be identified (8). Mild TBIs, or concussions, comprise the majority of TBIs that occur annually (2). A blow, bump, or jolt to the head, as well as a blow to the body, can result in mild TBI. These abrupt movements cause the brain to bounce or twist within the cranium, causing chemical changes in the brain and neuronal injury. Cell death following TBI is influenced by neuroinflammation and apoptosis (16). Drugs with anti-apoptotic, anti-inflammatory, and free radical scavenger-like pharmacological effects are known to be effective in TBI treatment (11,16,31).

Ginger (Zingiber officinale) roots and extracts, which have been used as a spice for 2000 years, contain polyphenolic compounds like 6-gingerol and derivatives with significant antioxidant activity (13,27). Furthermore, studies have shown that ginger possesses antioxidant, anti-inflammatory, and potential anticancer properties (13,26,27,32). The active compounds gingerol, shogaol, zingerone, and essential oils contained in ginger (family Zingiberaceae) exhibit anti-inflammatory, antioxidant, cardiovascular disease prevention, and anticancer activity. It has been demonstrated that administering 50 mg/kg i.p. of ginger extract following a TBI decreased NF-κB, IL-1β, and GFAP levels and increased BDNF, GAP, and Nrf2 levels (24). In recent years, there has been an increase in the usage of bioactive compounds, including curcumin, ginger, epigallocatechin gallate, resveratrol, soya isoflavones, lycopene, and naringin (25). These antioxidant compounds exhibit neuroprotective and therapeutic effects involving anti-inflammatory pathways (19,23). The effects of ginger, rich in phenolic compounds such as trans-6-shogaol and 6-gingerol, which are known to have neuroprotective effects on motor and cognitive functions after mTBI, and its relationship with neuroinflammation have not been thoroughly elucidated (19,23). Furthermore, we investigated the neuroprotective properties of ginger treatment prior to mTBI as a prophylactic measure for at-risk individuals. Consequently, the objective was to reduce the extent of the harm that at-risk individuals for recurrent head trauma will sustain because of their professional or athletic careers.

MATERIAL and METHODS

Fifty 3-month-old male Wistar Albino rats were divided into five groups: Control, Ginger, TBI, TBI+Ginger, and Ginger+TBI (n=10 per group) (Figure 1). The rats in the control and TBI groups were administered ginger extract (10% ginger extract (5 g) solution in ethanol [50 mL]) intraperitoneally (i.p.). The mTBI model was developed using the Marmarou method (17). The rats in the Ginger, TBI+Ginger, and Ginger+TBI groups were administered 50 mg/kg ginger extract i.p. for TBI treatment (24). In the Ginger+TBI group, the ginger treatment was initiated two days before the TBI, and 50 mg/kg ginger extract (i.p.) was administered for four days. The ginger treatment was initiated at the second hour of TBI in the ginger and TBI+Ginger groups, and 50 mg/kg ginger extract was administered i.p. for two days. The motor function was evaluated using the open-field test (OF), while the cognitive

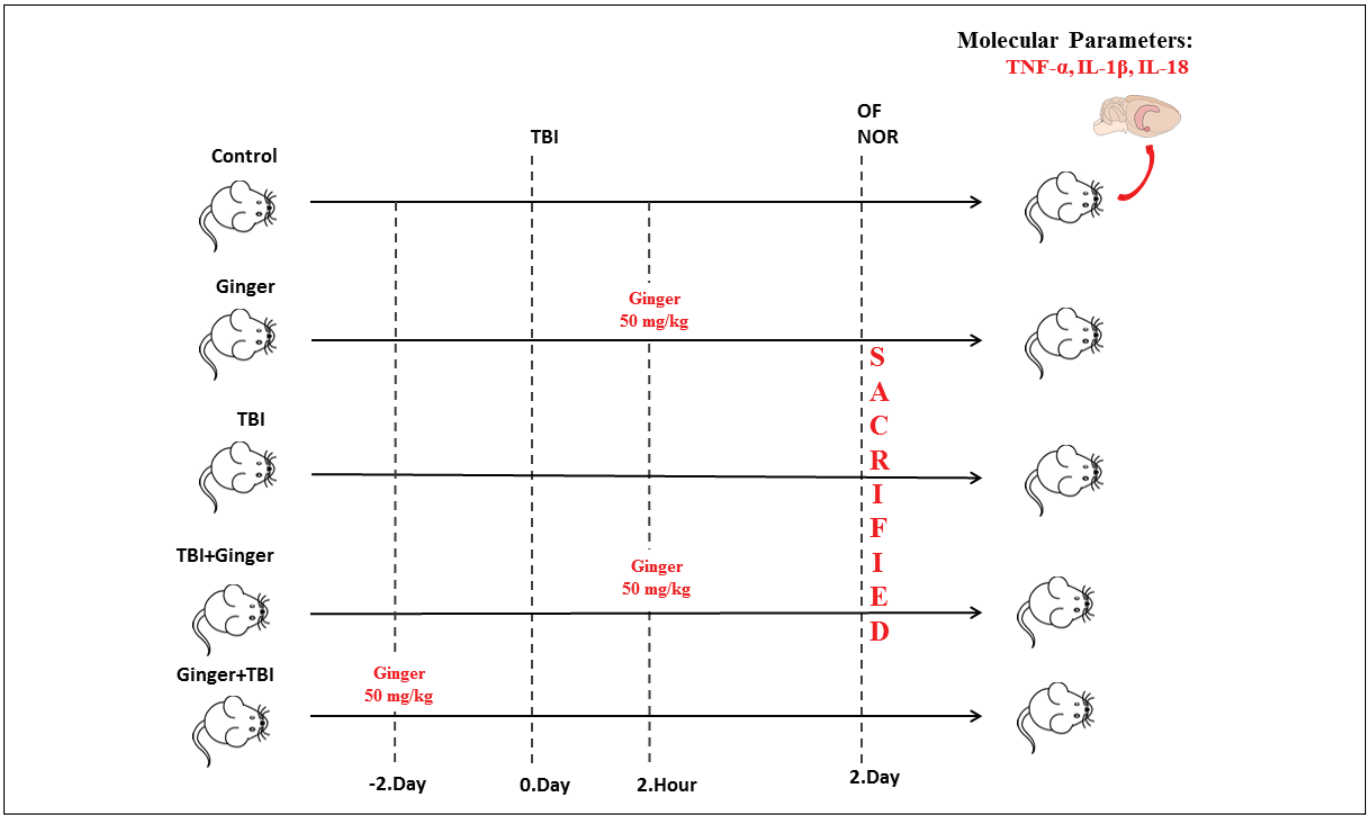

Figure 1: Experimental design of the study.

function was assessed employing the novel object recognition test (NOR). Experiments were conducted to determine the cytokine levels (IL-1β, TNF-α, and IL-18) in the hippocampus tissue.

This study was approved by the Erciyes University institutional review board (approval no. 22/136, dated 01.06.2022).

Marmarou Weight Drop Model

Marmarou's weight drop method was employed for developing the mTBI model (17). We employed the mTBH protocol in our model, as we had done in our previous study (4,15,18).

OF

The OF test is a behavioral experiment involving the evaluation of locomotor activity. In the experimental protocol, processes implemented in our previous studies were used (3,5). The total distance (cm) and frequency parameters were utilized to evaluate motor function (5).

NOR

The NOR test is often preferred for estimating attention or short-term memory-related activities. The experimental protocol employed the same procedures as our previous investigations (1). In the NOR test, the discrimination index and the time spent on the novel object (sec) values were analyzed.

Protein Measurements

The protocols employed in our previous investigations were used to homogenize hippocampal tissues and measure protein concentration.

Biochemical Analysis

ELISA

The experimental protocols employed in our previous studies were used for evaluating TNFα, IL-1β, and IL-18 levels utilizing the ELISA method (1).

Gas Chromatography-Mass Spectrometry (GC-MS) analysis

In GC-MS measurements, the experimental protocols used in our previous studies were used after modifications (21,28). The ginger extract was obtained using the soxhlet apparatus in accordance with methods described in previous literature (21). In the current study, forty-six volatile phenolic components were identified in ginger samples from Çorum, Turkey. In the 63 minutes of scan duration, components corresponding to five peaks observed consistently in all chromatograms (Figure 2) were identified and designated as the most abundant components in ginger extract. Table

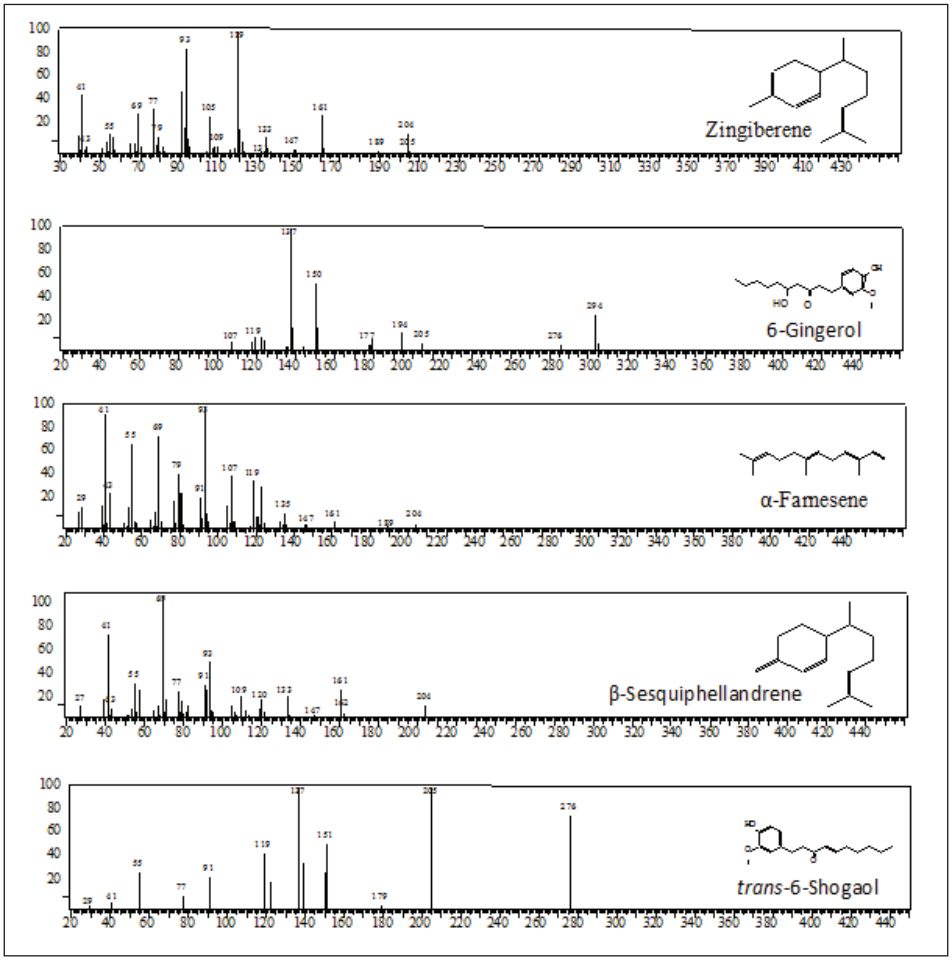

Figure 2: GC-MS chromatograms of the predominant ginger extract components.

I illustrates all these components. The GC-MS analyses revealed that ginger extract contained a significant amount of 6-gingerol (6.37%), *trans*-6-shogaol (13.34%), zingiberene (18.18%), β-sesquiphellandrene (10.26%), and (E, E)-α-Farnesene (6.05%), which significantly accounted for ginger's aroma. 6-shogaol, a component of ginger, has been reported to have several pharmacological properties, such as anti-inflammatory, antipyretic, antitussive, and hypotensive effects, as well as anti-inflammatory and antioxidant effects on neurons (6,7,19,22). It has been established that ginger extract has a neuroprotective effect because of its antioxidant properties (20). Ginger contains components with antioxidant activity, including shogaols and zingerones, which can scavenge free radicals, prevent cytokine secretion, and suppress cell death (4).

Statistical Analysis

Initially, we implemented the Shapiro-Wilk test to verify the normality of the data. The results exhibited a normal distribution and were evenly dispersed. The data are expressed as the mean ± SEM. Using one-way ANOVA followed by and Tukey's post hoc test. The data were considered significant only at $p<0.05$.

Table I: Identified Components of the Ginger Extract

No	Compound	Formula	RT min.	% Area	Ret Index	Familia
1	1,3-Butendiol	$C_4H_{10}O_2$	5.192	0.68	0	Alcohol
2	endo-Borneol	$C_{10}H_{18}O$	18.714	0.87	1138	Terpenes
3	α-Terpineol	$C_{10}H_{18}O$	19.668	0.33	1143	Terpenes
4	(-)-β-Chamigrene	$C_{15}H_{24}$	29.185	0.37	1507	Sesquiterpenes
5	R-α-curcumene	$C_{15}H_{22}$	29.873	2.05	1480	Aromatic monoterpenoids
6	S-α-curcumene	$C_{15}H_{22}$	29.983	4.22	1524	Aromatic monoterpenoids
7	Zingiberene	$C_{15}H_{24}$	30.474	18.18	1496	Monocyclic sesquiterpene
8	(E,E)-α-Farnesene	$C_{15}H_{24}$	30.775	6.05	1458	Sesquiterpenes
9	β-Bisabolene	$C_{15}H_{24}$	30.825	2.40	1500	Sesquiterpenes
10	β-Sesquiphellandrene	$C_{15}H_{24}$	31.329	10.26	1523	Sesquiterpenes
11	α-Patchoulene	$C_{15}H_{24}$	31.493	0.41	1459	Triterpene
12	*trans*-Nerolidol	$C_{15}H_{26}O$	32.415	0.74	1564	Sesquiterpenes
13	Dodecanoic acid	$C_{12}H_{24}O_2$	32.548	0.41	1570	Saturated fatty acid
14	Guaiol	$C_{15}H_{26}O$	34.370	0.43	1614	Sesquiterpenoid alcohol
15	Caryophyllene oxide	$C_{15}H_{24}O$	34.437	0.58	1507	Terpenes
16	Zingerone	$C_{11}H_{14}O_3$	34.956	0.49	1638	Phenolic
17	β-Eudesmol	$C_{15}H_{26}O$	35.121	0.57	1656	Terpenes
18	α-Eudesmol	$C_{15}H_{26}O$	35.210	0.49	1598	Terpenes
19	α-Bisabolol	$C_{15}H_{26}O$	35.304	0.59	1688	Sesquiterpene alcohol
20	(R, R)-α-Bisabolol	$C_{15}H_{26}O$	35.463	0.27	1625	Sesquiterpene alcohol
21	β-bisabolol	$C_{15}H_{26}O$	35.620	0.40	1619	Sesquiterpene alcohol
22	Bicyclo (4.3.0) nonane, 2,2,6,7-tetramethyl-7-hydroxy-	$C_{13}H_{24}O$	35.894	0.26	0	Sesquiterpenoids
23	*E*-Nerolidol	$C_{15}H_{24}O$	36.398	1.56	1572	Sesquiterpene alcohol
24	2-Cuparenol	$C_{15}H_{22}O$	37.924	0.24	1776	Phenolic
25	Campherenone	$C_{15}H_{24}O$	39.512	0.79	0	Terpenes
26	2-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-pentane-2,3-diol	$C_{15}H_{24}O$	39.721	0.26	1776	Terpenes

Table I: Cont.

No	Compound	Formula	RT min.	% Area	Ret Index	Familia
27	Campherenone	$C_{15}H_{24}O$	41.136	0.46	0	Terpenes
28	geranyl-*p*-cymene	$C_{20}H_{30}$	43.303	0.42	2006	Terpenes
29	*n*-Hexadecanoic acid	$C_{16}H_{32}O_2$	43.602	2.61	1968	Saturated fatty acid
30	geranyl-.alpha.-terpinene	$C_{20}H_{32}$	43.991	0.32	1962	Terpenes
31	(-)-Nortrachelogenin	$C_{20}H_{22}O_7$	47.124	0.35	1328	Phenolic
32	9,12-Octadecadienoic acid (Z,Z)-	$C_{18}H_{32}O_2$	47.770	2.72	2183	Fatty Acid
33	7-Tetradecenal, (Z)-	$C_{14}H_{26}O$	47.884	1.50	1609	Fatty aldehyde
34	Geranyl linalool	$C_{20}H_{34}O$	48.044	0.59	2046	Terpene alcohol
35	Octadecanoic acid	$C_{18}H_{36}O_2$	48.326	0.61	2167	Fatty Acid
36	(4-Methoxy-phenyl)-(2-nitrocyclohexyl)-methanol	$C_{14}H_{19}NO_4$	49.701	1.63	2148	Aromatic terpene
37	Zingerone	$C_{11}H_{14}O_3$	49.896	1.01	1638	Phenolic
38	*trans*-6-shogaol	$C_{17}H_{24}O_3$	51.468	13.34	0	Phenolic
39	ZO-3-(6)-Gingerdione	$C_{17}H_{24}O_4$	52.121	1.03	0	Phenolic
40	Butanoic acid, 3,7-dimethyl-2,6-octadienyl ester, (E)-	$C_{14}H_{24}O_2$	52.350	0.33	1550	Terpenes
41	6-Gingerol	$C_{17}H_{26}O_4$	53.518	6.37	2396	Phenolic
42	Carinol	$C_{20}H_{26}O_6$	55.599	0.79	3296	Phenolic
43	*cis*-8-shogaol	$C_{19}H_{28}O_3$	56.163	4.43	0	Phenolic
44	(E)-4-(2',6',6'-Trimethyl-1',2'-epoxycyclohexyl)-3-penten-2-one	$C_{14}H_{22}O_2$	57.175	0.62	0	Terpenes
45	Gingerol	$C_{17}H_{26}O_4$	59.208	0.68	2396	Phenolic
46	1-(2,4-Dihydroxyphenyl)-2-(4-methoxy-3-nitrophenyl)ethanone	$C_{15}H_{13}NO_6$	60.299	1.22	2728	Phenolic

RESULTS

During the OF test, the rats' motor function was evaluated, and the NOR test evaluated their learning skills (Figure 3). The motor function in the OF test was significantly decreased in the TBI group rats compared to the control group ($p<0.05$) (Figure 3A). In comparison to the TBI group, the Ginger+TBI and TBI+Ginger group rats exhibited a substantial improvement in motor function following ginger treatment ($p<0.05$) (Figure 3A-B). The short-term memory of the rats was evaluated using the NOR test (Figure 3C). While the learning of the TBI group rats was significantly reduced in comparison to the control group ($p<0.05$), the Ginger+TBI and TBI+Ginger group rats exhibited a significant increase when compared to the TBI group rats ($p<0.05$).

DISCUSSION

TBI is a significant cause of motor and cognitive impairment and is a leading cause of disability worldwide (2). Anti-inflammatory drugs, anti-apoptotic drugs, and free radical scavengers have been examined as potential treatments for TBI. Antioxidants have been shown to reduce glial activation and inflammatory responses when employed for treating TBI. Patients with TBI experience loss of movement and cognitive function, especially at later ages. It is fatal, disabling, and requires long-term therapy and care. Thus, the prophylactic measures are clinically beneficial for individuals at high risk of mTBI. Thus, this study examined the therapeutic and neuroprotective effects of prophylactic ginger administration in a mTBI rat model to determine its efficacy in patients at high risk of mTBI.

Diminished locomotor activity in animals may be interpreted as a loss of motor function. Certain studies have revealed that TBI causes motor function loss (10,12,29). Kim and Han have demonstrated that TBI causes motor function loss in rats (14). The current study results revealed that TBI induced motor function loss, while ginger treatment enhanced motor function. Ginger treatment, when administered prior to TBI,

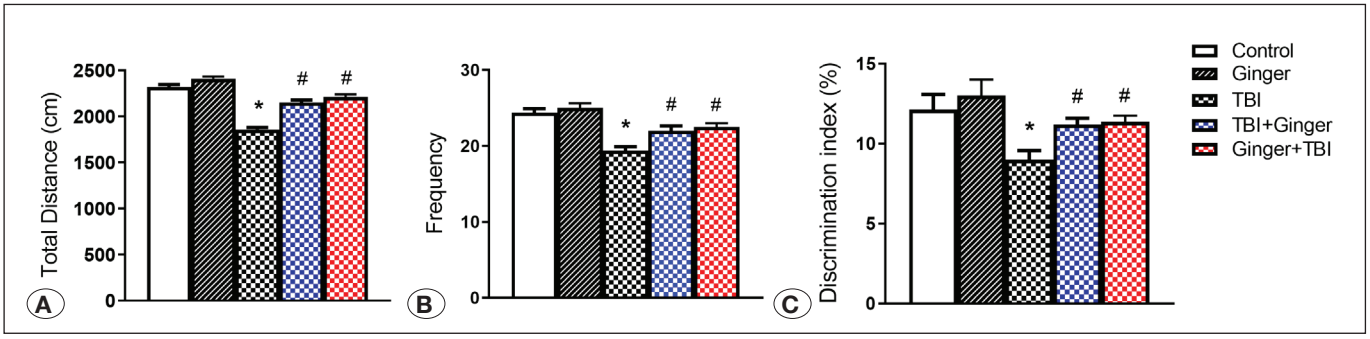

Figure 3: Motor and cognitive function test results. **A)** Total distance (cm) results; **B)** Frequency results; and **C)** Discrimination index results.

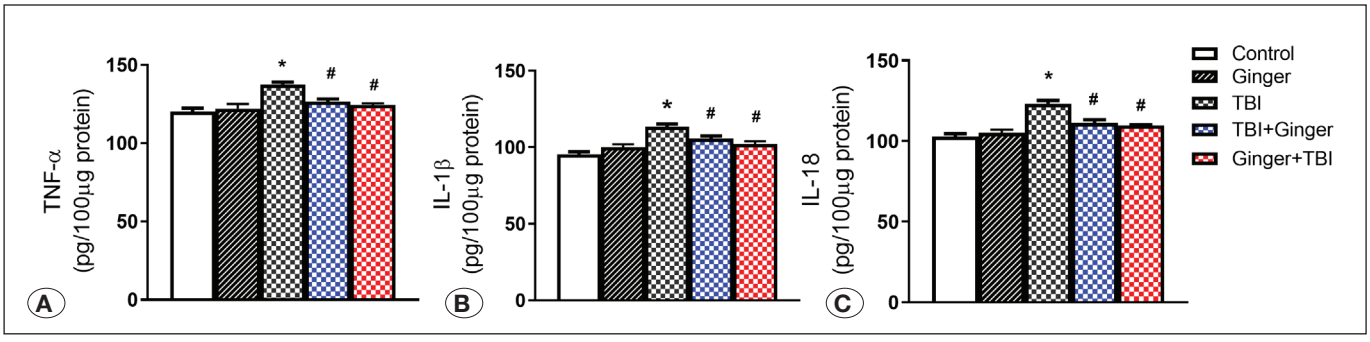

Figure 4: Hippocampal cytokine levels. **A)** TNF-α levels; **B)** IL-1β levels; and **C)** IL-18 levels.

was determined to be crucial for motor function restoration. The study also concluded that TBI causes loss of cognitive function, while ginger treatment mitigates learning impairment. According to the cognitive function results, mTBI resulted in learning impairment, and the discrimination index of the TBI group decreased in comparison to the control group. Ginger treatment was found to reduce cognitive loss when administered both before and after TBI. In particular, it was noted that the curative effect of preventive ginger treatment prior to mTBI was superior.

TBI causes free radical generation and elevated cytokine levels. Antioxidant treatments are recognized for their ability to mitigate neuroinflammation following TBI. It has been shown that 50 mg/kg i.p. ginger treatment after TBI reduces neuroinflammation and exhibits a neuroprotective effect (24). In our study, mTBI resulted in an increase in IL-1β, TNF-α, and IL-18 levels in hippocampal tissue. The IL-1β, TNF-α, and IL-18 levels in the TBI group were increased compared to the control group. The neuroinflammation induced by TBI was reduced through 50 mg/kg (i.p.) treatment in our study. Ginger treatment before and immediately after TBI reduces IL-1β, TNF-α, and IL-18 levels. More specifically, the active phenolic components in the 50 mg/kg ginger treatment that was administered prior to TBI were found to be effective in reducing neuroinflammation. This treatment is clinically desirable due to its prophylactic efficacy in individuals at high risk for TBI. Head traumas cause motor and cognitive function loss, especially at later ages, are fatal, disabling, and necessitate long-term treatment and care.

For the first time in the literature, ginger extract was administered prior to mTBI in our study for protective purposes, as illustrated in the experimental schedule in Figure 1. This was done to safeguard individuals who are at risk of experiencing TBI. This study demonstrated that mTBI induces motor and cognitive function loss and impacts neuroinflammation levels. Furthermore, it has been demonstrated that ginger treatment, when administered before and after brain damage, offers protective and therapeutic benefits in motor cognitive function loss due to the effect of phenolic components. The antioxidant effect of gingerol and shogaol, which were isolated from ginger, improved the reduced motor function that was caused by mTBI. Additionally, ginger treatment administered before and after mTBI was observed to reduce cytokine levels, which was attributed to the effect of phenolic compounds, including *trans*-6-shogaol and 6-gingerol.

Limitations

This study only examined the short-term therapeutic efficacy of ginger. However, the long-term clinical efficacy of ginger treatment is also known, and this restricts the study. Additionally, the study did not account for the beneficial impact of the other compounds in the ginger extract, which are present in minute quantities, on the treatment of mTBI. Terpenoids, sesquiuterpenes, lactones, and ketones, other than the phenolic components contained in ginger extract, have been found to affect TBI treatment (9,11). In our study, it was presumed that the predominant phenolic components, such as *trans*-6-shogaol (13.34%) and 6-gingerol (6.37%), in

ginger extract were responsible for its therapeutic efficacy in mTBI treatment. However, the treatment of mTBI may be beneficially affected by other components of ginger extract, which are present in minor quantities and interact with IL-1β, TNF-α, and IL-18. In future studies, both male and female mice may be included, and shogaol and ginger may be procured for comparison with ginger extract.

CONCLUSION

The GC-MS analysis detected 46 components in ginger extract, the most common of which are zingiberen (18.18%), *trans*-6-Shogaol (13.34%), β-Sesquiphellandrene (10.26%), 6-gingerol (6.37%), and (E, E)-α-farnesene (6.05%). The therapeutic effect of ginger extract before and immediately after mTBI, as well as its distinct effect on motor and cognitive function and neuroinflammation, is thought to be due to 6-gingerol and *trans*-6-shogaol. In particular, treatment with shogaol and gingerol-rich ginger, before mTBI was found to reduce locomotor activity loss. Due to phenolic components such as gingerols and shogaols in ginger treatment, it reduced learning disability by regulating hippocampal cytokine levels. The study findings demonstrated that the long-term effects on chronic mTBI may be determined by isolating components such as *trans*-6-Shogaol or 6-Gingerol from the ginger extract through chromatographic techniques. According to our current understanding, the administration of ginger extract prior to mTBI is more effective in regulating neuroinflammation. Consequently, it may serve as a treatment option for high-risk mTBI patients by expediting the improvement of motor function and cognitive impairment. By examining the efficacy of prophylactic ginger treatment, this study demonstrated its importance and it may be considered as a treatment option that is supported by more studies.

ACKNOWLEDGEMENTS

In 2025 In Honor of Prof. Dr. M. Gazi Yaşargil's 100th Birthday

This article is dedicated to Prof. Dr. M. Gazi Yaşargil, one of the pioneers of modern neurosurgery, who left an indelible mark on the medical world with his extraordinary contributions to the field, on the occasion of his 100th birthday. Prof. Dr. Yaşargil revolutionized the application of microsurgical techniques in neurosurgery, opening a new era in neurosurgery. He is recognized as one of the pioneering leaders not only in Turkey but also in the world medical community. Prof. Dr. Yaşargil's work has contributed not only to the development of surgical techniques but also to improving the quality of life of patients. In this context, this article is dedicated to our esteemed professor in celebration of his 100th birthday and as a reminder of his unique contributions to the world of science.

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: GA, SO
Data collection: GA, SO
Analysis and interpretation of results: GA, AY, SO
Draft manuscript preparation: GA, SO
Critical revision of the article: GA, FD, SO
Other (study supervision, fundings, materials, etc...): GA, FO, SO
All authors (GA, FO, SO, AY, FD) reviewed the results and approved the final version of the manuscript.

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