Original Article

Intralipid and Caffeic Acid Phenethyl Ester Reverse the Neurotoxic Effects of Organophosphate Poisoning in Rats

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Abstract

Background: Organophosphate (Op)-containing herbicides continue to be widely used in the world. Although its usage and intoxication are widespread, the studies on organophosphate-induced neurotoxicity and treatment protocols are very few in the literature. **Aims:** This study aimed to investigate any potential effects of caffeic acid phenyl ester with/without intralipid on neurotoxicity produced by acute intoxication of glyphosate isopropylamine in an experimental rat model. **Materials And Methods:** Forty-nine wistar albino rats were randomly allotted into seven experimental groups: I, control; II, intralipid (IL); III, caffeic acid phenyl esther (CAPE); IV, glyphosate isopropylamine (GI); V, GI + IL; VI, GI + CAPE; and VII, GI + IL + CAPE. Total antioxidant and oxidant status levels were gauged, and the oxidative stress index was calculated in the serum samples. On the other hand, the tissues were analyzed with hematoxylin-eosin (HE) staining protocol and counted up by immunohistochemical method. Statistical evaluations were conducted using SPSS 11.5 for Windows (SPSS, Chicago, IL, USA). **Results:** Compared to the control, IL, and GI + IL + CAPE groups, the GI group significantly decreased the total antioxidant levels in brain tissues. In a supportive nature, a significant increase in the oxidative site index (OSI) in the GI group compared to other groups. Especially standing out point of these findings is the significant difference between the GI + IL + CAPE and the GI group. Parallelly, histopathological analysis extended severe neurotoxicity in the GI group. Neurotoxic status was reduced significantly in the GI + CAPE + IL group. The histopathologic examinations confirmed biochemical results. The results also revealed that CAPE and IL, probably their antioxidant effects, have a rehabilitative effect on neurotoxicity caused by GI. **Conclusion:** Therefore, CAPE and IL may function as potential cleansing and scavenger agents for supportive therapy regarding tissue damage or facilitate the therapeutic effects of the routine treatment of the patient with GI poisoning.

Keywords: *Caffeic acid phenethyl ester, glyphosate isopropylamine, intralipid, neurotoxicity, organophosphates*

Introduction

Glyphosate, usually formulated as an isopropylamine salt, is an organophosphate (Op) compound and a broad-spectrum systemic herbicide or weed desiccant targeting broadleaf weeds, grasses, and woody plants. The agricultural sector has predominantly used glyphosate isopropylamine (GI) to kill pernicious weeds without killing their healthy flora since the 1970s. Also, increasing demand for the recreation of house lawns, yards, parks, golf courses, and swimming pools results in a hundred-fold more consumption in frequency and

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volume worldwide, with further proportional increases expected. Widespread usage and easy access inevitably give rise to environmental pollution and a large amount of intoxication. It is the most common reason for poisoning entering the emergency department annually. Victims of GI poisoning require immediate hospital emergency room treatment to avoid a fatal outcome or ensuing numerous hundred thousand in morbidity and mortality.[1-3]

Intralipid (IL) (liposyn 20%) have routinely been used in parenteral nutrition therapy and widely accepted to be effective in reversing the toxic effects of lipid-soluble drugs such as propranolol, bupropion, and haloperidol. Similarly, a few cases reported its beneficial effects in resuscitating excessive local anesthetic drug toxicity. Although the exact mechanisms of its antidotal action are unclear, the "lipid sink" mechanism might refer to a reasonable explanation. Much lipids in the blood can move the fat-soluble drugs away from the toxicity site and dissolve them in the plasma, which might ease the poisonous impact of the fat-soluble drug. Fat-soluble agents, such as the GI, can be retained, lowering their concentration within tissues using the IL and reducing toxicity.[4]

Caffeic acid phenethyl ester (CAPE) is a chemical compound naturally found in many plants and an active substance of propolis from honeybee hives. Plenty of recent studies have reported on CAPE pharmacological and *in vivo* various effects in animal models. Although the clinical significance is unclear, it has antimitogenic, anti-carcinogenic, anti-inflammatory, and immunomodulatory properties. The anti-cancer effect was especially seen when the skin papillomas of mice were treated with bee propolis. CAPE significantly reduced the number of papillomas.[5] Additionally, particular attention has been focused on understanding the mechanisms underlying antioxidant properties. The still growing concern on CAPE, capable of counteracting the effects of oxidative stress underlying the pathogenesis of numerous diseases, such as neurodegenerative disorders, cancer, diabetes, and atherosclerosis, is being observed. Propolis also activates various antioxidant enzymes, such as superoxide dismutase and catalase, against free radicals.[5] The antioxidant activity of propolis extract is specially attributed to its ability to scavenge free radicals and thereby protect against lipid peroxidation.[6]

Reactive oxygen species (ROS) are cell signaling molecules for normal biologic processes. However, the generation of ROS can also provoke damage to multiple cellular organelles and processes, which can ultimately disrupt normal physiology. An imbalance between the production of ROS and the antioxidant defenses that protect cells has been implicated in the pathogenesis of Op poisoning, as with the molecular basis of many diseases. Most widely used pesticides create their neurotoxicity by altering the balance between ROS production and the ability of the organism's antioxidant system to neutralize them. The nature of the injury will ultimately depend on specific molecular interactions, cellular locations, and the timing of the insult.[7]

This study will outline the effect of IL and CAPE on scavenging excessive ROS that may be endogenously generated in neural tissues exposed to organophosphate poisoning, thus contributing to the treatment process. We aimed to determine whether they have potential therapeutic effects and may benefit from this antidotal therapy.

Materials and Methods

Animals care

Adult female wistar albino rats (weighed 210–260 g) were kept under appropriate laboratory conditions through a 12-hour light-dark cycle and a room temperature of 22 ± 3°C. They were ambulated freely for socializing, eating, and drinking and observed in a couple of weeks, examining daily routine before treatment. The grant of the scientific research project at Mustafa Kemal university, Hatay-Turkey, provided all rats used in this study. Ethical approval was obtained from the experimental animals ethics committee at Necmettin Erbakan university, Konya-Turkey.

Animal treatment

A total of forty-nine animals were allotted into seven different groups, having seven animals each: 1-control (C), 2-glyphosate isopropylamine (GI) (4 mg/kg/day orally), 3-intralipid (IL) (18.6 mL/kg, orally), 4-caffeic acid phenethyl ester (CAPE) (10 μmol/kg, intraperitoneally), 5-IL plus GI, (IL + GI), 6-CAPE plus GI (CAPE + GI), and 7-IL plus CAPE plus GI (IL + CAPE + GI). Intralipid and CAPE were injected ten minutes after GI application, and then the rats were decapitated by following ketamine (50 mg/kg; intraperitoneal) and xylazine (5 mg/kg, intraperitoneally) anesthesia. All brain tissues were removed and longitudinally divided into two pieces. Half was used for biochemical assays, and the other for histopathological evaluations. Blood samples were taken out directly by cardiac puncture, and the supernatants were drawn after centrifugation and stored at −80°C. Total oxidant status (TOS) and total antioxidant status (TAS) levels were measured in the serum samples.

Biochemical analysis

Serum TAS levels were measured by an automatic and colorimetric method developed by Erel. This method

provides excellent precision values lower than three percent. The TAS results were written as nmol Trolox equivalent/mg protein, and the TOS levels were expressed as nmol H2O2 equivalent/mg protein. The oxidative site index (OSI) was defined as the TOS to TAS level ratio and calculated as OSI = TOS (μmol H2O2 Eq/L)/ TAS (μmol Trolox Eq/L). This parameter is significantly associated with the severity of toxic effects.[8,9]

Immunohistochemistry (IHC)

Immunohistochemical evaluation was completed using a Leica Bond-Max automatic (immunohistochemistry) IHC/ISH (in situ hybridization) platform. Four-micrometer paraffin sections were taken wax out in a Bond dewax solution and rehydrated in alcohol and Bond wash solution. The retrieval of antigens was performed by using a high-pH retrieval solution for 15 min that was followed by endogenous peroxidase blocking for five min on the device. The applications of anti-mouse monoclonal antibody Bcl-2 (C-2: sc-7382, Santa Cruz Biotechnology, Inc., in dilution 1:200), anti-mouse monoclonal antibody Bax (B-9: sc-7480, Santa Cruz Biotechnology, Inc., in dilution 1:100), anti-mouse caspase-3, and monoclonal antibody were performed at the rate of 1:50 dilution for 60 min at room temperature. A Bond polymer refine red detection system was used for detection with a 15-min post-primary step followed by the incubation with alkaline phosphatase-linked polymers for 25 min. Afterward, the sections were counterstained with hematoxylin, dehydrated in alcohols, and established with the mounting medium. Two histopathologists blinded to the experimental groups monitored the preparation stage of the tissues. Ten randomly decided microscope fields were analyzed under 400× magnification in a blind style to count the apoptotic cells.

Histopathological analysis

Hematoxylin and eosin (H and E) procedure

The tissues were first submerged into a solution containing 10% formaldehyde and then embedded into paraffin blocks. A microtome was used to cut four-micron sections from blocks. All the tissues were stained with H and E by using routine protocols. Whole slides were analyzed by an Olympus BX51 microscope (Tokyo, Japan).

Histopathologic examination of the brain

Signs of inflammation, congestion, necrobiosis, and necrosis were examined in the frontal cortex. In the histopathological section evaluation of the brain, inflammation (1-yes, 0-none), vascular congestion (0-none, 1-mild, 2-moderate, 3-pronounced), and necrobiotic/ necrotic changes (0-none, 1-mild-moderate necrobiosis, 2-prominent necrobiosis, 3-mild-moderate necrosis, 4-prominent necrosis) were scored semiquantitatively.

Statistical evaluation

Data were defined as mean ± standard error of the mean (SEM). Statistical evaluations were conducted using SPSS 11.5 for Windows (SPSS, Chicago, IL, USA). Normal distributions were confirmed by a one-way ANOVA is a statistical test which stands for Analysis of Variance, can be left as a ANOVA. A P value of < 0.05 was considered significant.

Results

TAS and TOS levels

In brain tissues, the TAS levels significantly decreased in the GI group, and TOS levels significantly increased in the GI group compared to other (C, IL, and GI + IL + CAPE) groups.

Table 1: Comparison of post-medication TAS, TOS, and OSI levels in brain tissues

	TAS	TOS	OSI
Control	0.93±0.09	11.99±2.01	12.98±2.77
CAPE	0.86±0.15	11.19±2.55	13.28±3.66
ILw	0.85±0.06	12.05±1.64	14.20±2.65
GI	0.63±0.09*	14.14±2.66	23.13±7.30*
GI + CAPE	0.84±0.06	12.86±2.78	15.31±3.59
GI + IL	0.76±0.09	12.82±1.25	16.96±2.96
GI+IL + CAPE	0.96±0.15^{+}	11.21±3.43	11.63±2.92^{+}

(GI)=glyphosate isopropylamine, IL=(intralipid), CAPE =(caffeic acid phenethyl ester). Data are presented as mean ± SD. The mean difference is significant at the level of 0.05 (P<0.05). *Compared with the GI group, the TAS values in the control, IL, and GI + IL + CAPE groups were significantly higher. *Compared with the GI group, the OSI values in control, IL, and GI + IL + CAPE groups were significantly lower. $^{+}$Compared with the GI + IL + CAPE group, the TAS values in the GI group were significantly lower. $^{+}$Compared with the GI + IL + CAPE group, the OSI values in the GI group was significantly higher

Table 2: Immunohistochemistry (IHC) and hematoxylin eosin (HE) scores of brain tissue comparison among all groups

	IHC	HE
Control	26.5±2.7	9.1±3.6
CAPE	33.6±2.6	7.1±2.4
IL	37.0±2.0	11.3±2.4
GI	217.8±3.4*	37.5±3.7^{+}
GI + CAPE	165.8±3.4	21.6±3.0
GI + IL	189.0±3.1	33.8±3.1
GI + IL + CAPE	170.2±3.4	22.6±3.4

Data were presented as mean ± SD. Values with mean difference (P<0.05) were evaluated statistically significant. * When we compared the GI group with the control, CAPE, IL, GI + CAPE, and GI + IL + CAPE groups, HE scores were significantly higher in the GI group. * When we compared the + GI group with the control, CAPE, IL, GI + CAPE, GI + IL, and *GI + IL + CAPE groups, IHC scores were significantly higher in the GI group. (glyphosate isopropylamine (GI), IL (intralipid), CAPE (caffeic acid phenethyl ester)

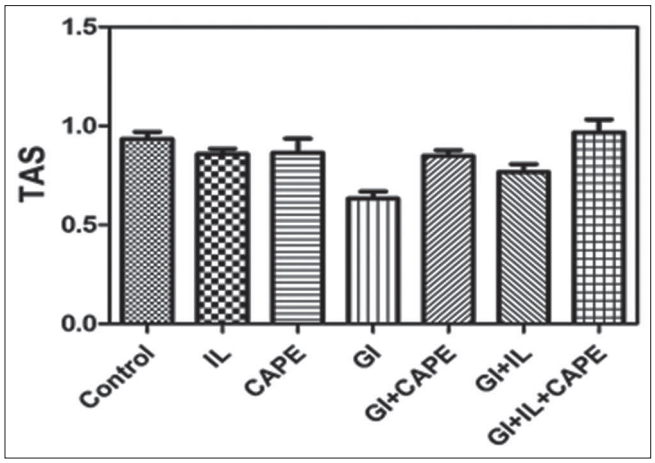

Figure 1: Comparison of TAS levels between groups

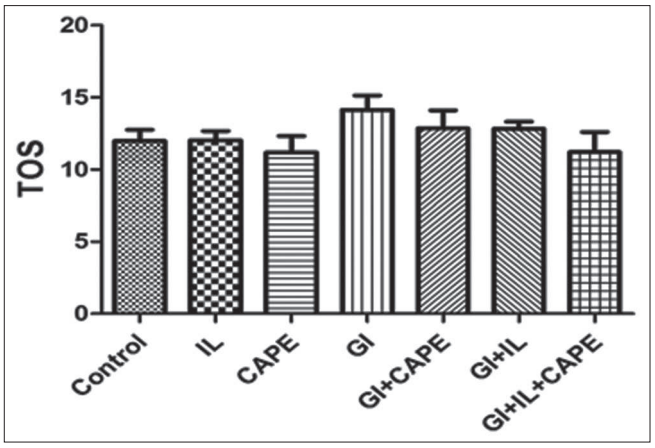

Figure 2: Comparison of TOS levels between groups

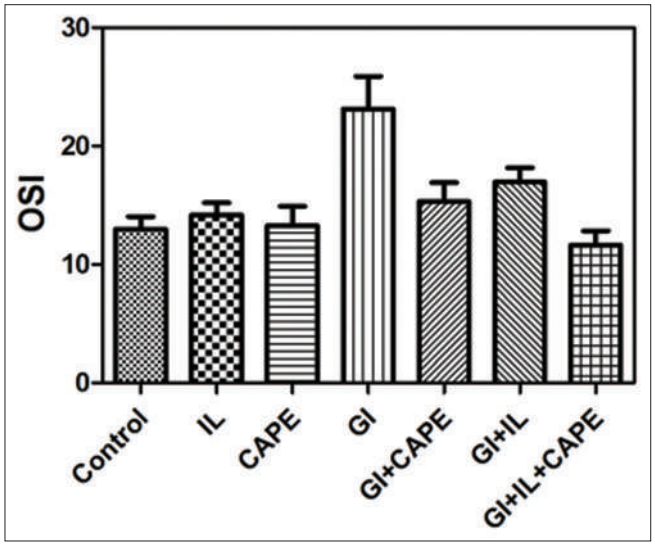

Figure 3: Comparison of OSI levels between groups

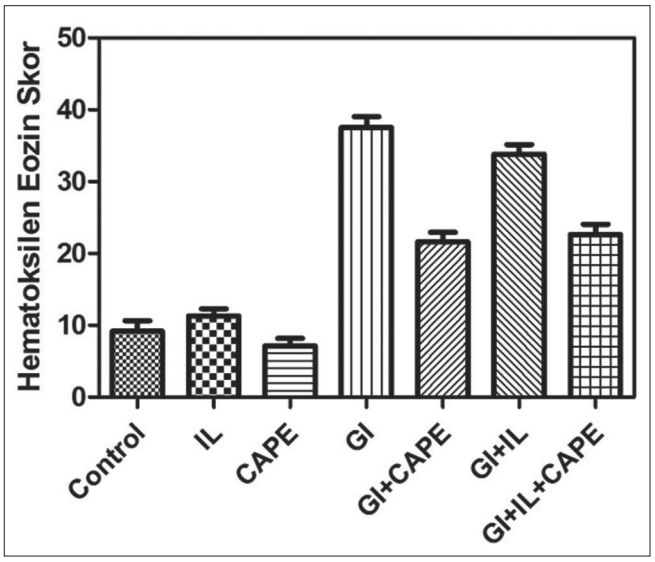

Figure 4: Comparison of hematoxylin eosin (HE) scores between groups

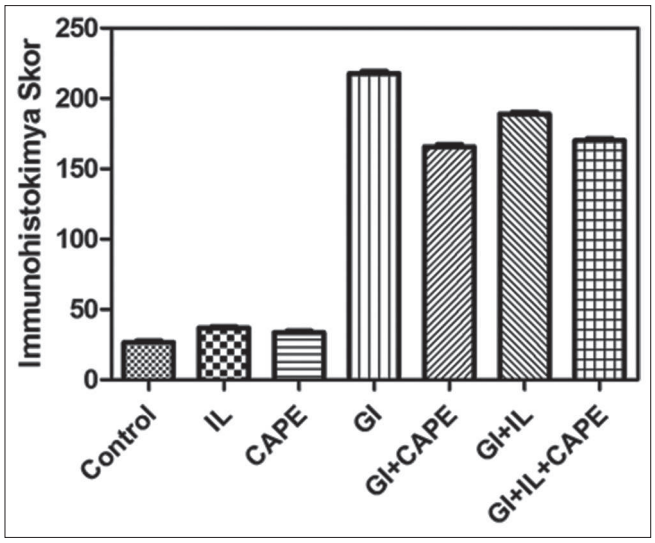

Figure 5: Comparison of intergroup IHC scores

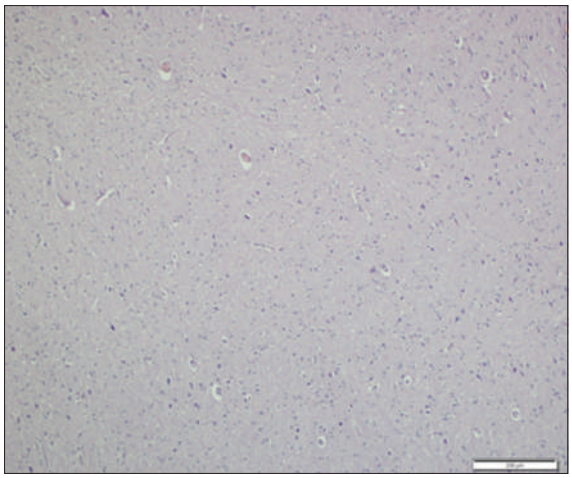

Figure 6: Normal histomorphological view of rat brain cortex tissue (H and E × 100)

Suitably, the GI group, compared to other groups, significantly increased the OSI. Among these findings, the significant difference between the GI + IL + CAPE and the GI group is found to be statistically meaningful [Table 1 and Figures 1-3].

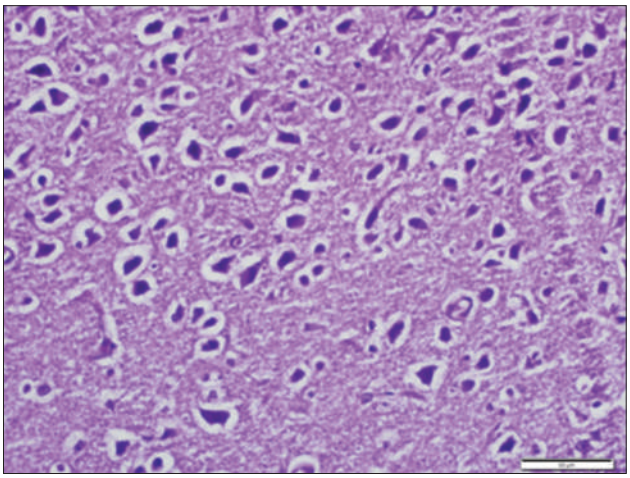

Figure 7: Vacuolar degeneration, dark pyknotic nuclei, and shrunken cytoplasms are observed (H and E, ×200)

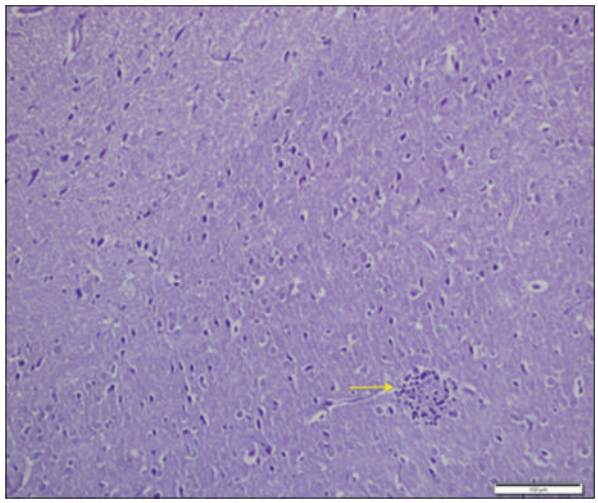

Figure 8: Inflammation is observed in the glial floor (H and E, ×200)

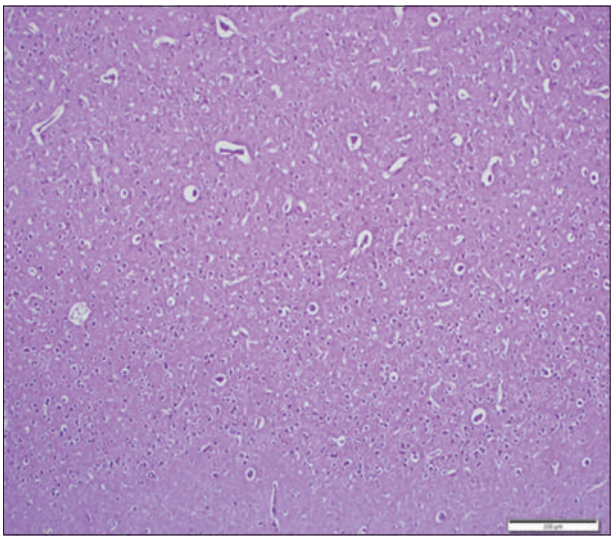

Figure 9: GI group, edema, congestion, and degenerative changes are seen together. (H and E, ×200)

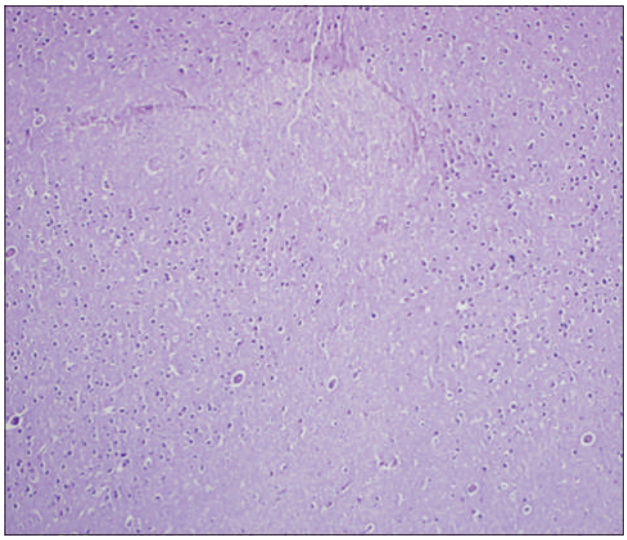

Figure 10: GI group, necrotic/necrobiotic changes showing severe damage are observed (H and E, ×200)

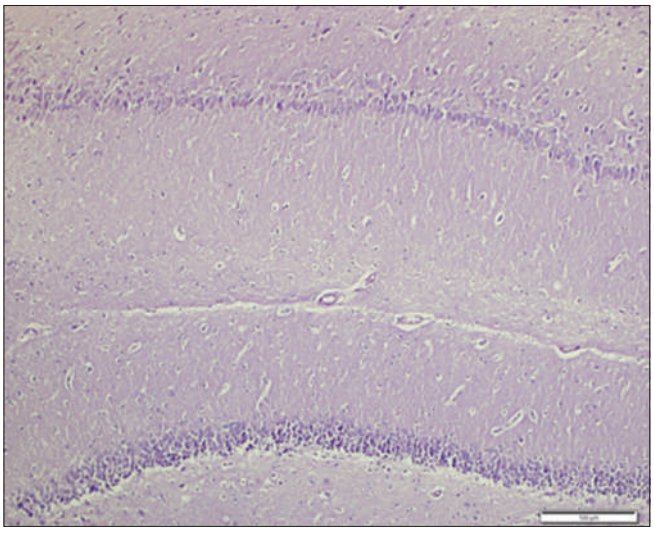

Figure 11: GI group, prominent necrosis is observed in the cerebellum (H and E, ×100)

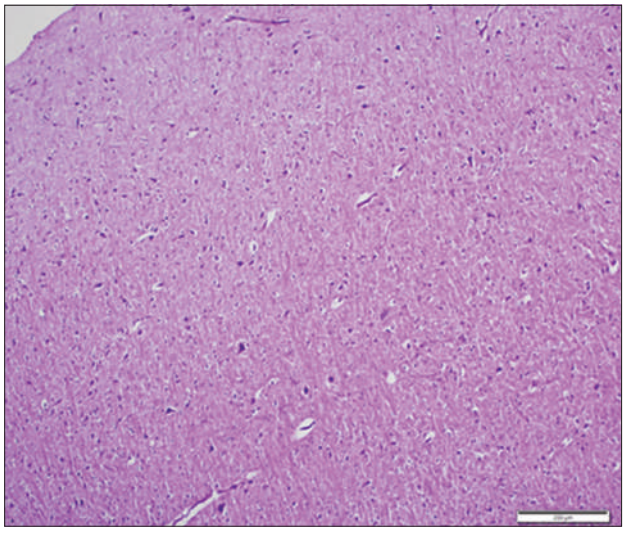

Figure 12: As a result of CAPE + IL application with GI (GI + CAPE + IL), histopathological improvement is almost complete (H and E, ×100)

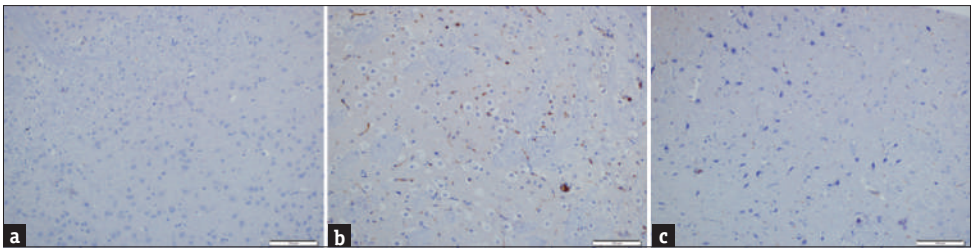

Figure 13: (a) Control group (IHC × 200), (b) GI group (IHC × 200), and (c) GI + CAPE + IL group, (IHC × 200)

Histopathologic Results

Brain

The control group also had a standard histomorphological view [Figure 6]. When comparing the GI group with the control group, vacuolar degeneration, dark pyknotic nuclei, and shrunken cytoplasms were observed in the GI group [Figure 7], and the GI group [Figure 8] showed inflammation in the glial floor. In addition, edema, congestion, and degenerative changes were seen together [Figure 9], and necrotic/necrobiotic changes showing severe damage were observed [Figure 10]. Significant necrosis was detected in the cerebellum [Figure 11]. However, due to CAPE + IL application with GI (GI + CAPE + IL), histopathological improvement was almost complete [Figure 12]. When comparing the GI group with the control, CAPE, IL, GI + CAPE, and GI + IL + CAPE groups, H and E scores were significantly higher in the GI group [Table 2 and Figure 4]. On immunohistochemical evaluation, In the control group, normal brain tissue [Figure 13a] increased apoptosis [Figure 13b] with GI application and moderate apoptosis [Figure 13c] with GI + CAPE + IL application. When comparing the GI group with the control, CAPE, IL, GI + CAPE, GI + IL, and GI + IL + CAPE groups, the fap scores were significantly higher in the GI group [Table 2 and Figure 5].

Discussion

Organophosphate-containing herbicides continue to be widely used in the world. Therefore, intentional or unintentional intoxications of humans are familiar. The primary target tissue of these agents is principally neural tissues. Early neurological involvement is an essential prediction of morbidity and mortality to lead to fatal results.[10] Although its usage and intoxication are widespread, the studies on GI-induced neurotoxicity and treatment protocols are very few in the literature. CAPE functions a broad spectrum of pharmacological activities with anti-inflammatory, antioxidant, and immunomodulatory properties and may have protective effects against neurotoxicity.[4] Similarly, a recent experimental study reported that IL, used in malathion poisoning, effectively reduces oxidative stress, especially in the acute period, and is described as a promising drug.[4] For this reason, we aimed to investigate the effects of natural agents such as CAPE and IL on GI-induced neurotoxicity in measuring TAS and TOS parameters. We also planned the study so they might rectify the toxic molecular environment. We also assessed apoptotic indicators, including caspase-3, Bcl-2, and Bax, by immunohistochemical analysis.

GI, a member of Op, is known to act by inhibiting the plant catalyst EPSP synthase (catalyst 5-enolpyruvylshikimic acid-3-phosphate synthase). This pathway is only found in prokaryotes such as bacteria, fungi, or algae but not observed in animals or humans. Moreover, GI has the most negligible affinity to inhibit the enzyme acetylcholinesterase in mammals among organophosphates and rarely causes symptomatic toxic clinical effects compared to others.[7] Therefore, it is the most preferred pesticide for controlling insect pests in agriculture. Although many studies in the literature report oxidative stress caused by Ops, very few investigate GI-induced toxicity. That why we choose this substance for the study. Several researchers reported that the level of GI-induced oxidative damage is parallel to a significant decrease in brain tissue TAS levels and a significant increase in TOS levels.[11-13] Our study also used a similar oxidative stress/balance indicator.

A study investigating cognitive dysfunction emphasized that the induction of oxidative stress and neuroinflammation were identified as significant contributors to such adverse effects, and systemic CAPE administration improved cognitive dysfunction caused by doxorubicin (DOX)-induced in Sprague-Dawley rats. Co-treatment with CAPE significantly counteracted DOX-induced behavioral and molecular abnormalities in rat brain tissues. Moreover, this experiment claimed that these results provide the first preclinical evidence for CAPE's promising neuroprotective activity against DOX-induced neurodegeneration and memory deficits.[13]

An experiment found that CAPE rescued the streptozotocin-induced memory loss through PI3-kinase

dependent pathway in rats and concluded that PI3-kinase mediated nitric oxide facilitation is an essential feature of CAPE modulation in streptozotocin-treated rats.[14]

The other study on organophosphate poisoning reported that acute chlorpyrifos administration emerged the intoxication, and CAPE and IL administration reduced its harmful effects. As a result of this study, CAPE and IL decrease in the severity of neurodegeneration and symptoms of Op intoxication. Our study also showed that GI application occurs neurotoxicity, and adding CAPE and IL reduces this neurotoxicity.[15]

A dose-dependent study suggested that both CAPE 10 and 20 doses afforded protection against DOX-mediated neuronal cell damage as evidenced by histopathological assessment and Nissl staining, and CAPE 20 dose exhibited a significantly greater degree of protection of hippocampal neurons viability than the CAPE 10 dose, as evidenced from assessing the levels of both Glial fibrillary acidic protein (GFAP) and tumor necrosis factor-alpha (TNF-α). It can be partly attributed to the more significant reduction in DOX-induced hippocampal neuroinflammation upon treatment with CAPE 20 compared to CAPE10. In conclusion, the present study provides preclinical evidence that CAPE could present a promising anti-amnestic and neuroprotective agent which could guard against DOX-induced cognitive impairment. The underlying mechanisms of neuroprotective activity include antioxidant, anti-inflammatory, and anti-apoptotic activities.[13]

A recent study suggested that IL administration is an effective treatment modality in patients who ingested sufficient glyphosate herbicide, expecting to bring about significant toxicity.[16] The other study reported that dichlorvos, an organophosphate, can induce apoptosis.[17] Another one declared that CAPE significantly restores the brain functions impaired by isoniazid and ethambutol.[7]

Compared to the control and other groups, the GI-only group significantly increased TOS and decreased TAS levels [Table 1]. However, there was no significant difference among the control and IL, CAPE, and GI + IL + CAPE groups regarding TOS and TAS levels.

However, in the case of combinations of the GI with CAPE or IL, changes in TOS and TAS levels that are indicatives of GI-induced toxic effects are suppressed. It is evidence that CAPE and IL can reverse GI-induced toxicity.

In light of these findings, CAPE and IL can decrease neurotoxicity, most likely through their antioxidant effects. Therefore, CAPE and IL or both can be added as supportive therapy to prevent brain damage and facilitate the therapeutic effects of the routine treatment modalities in patients with GI intoxication. The combined usage for brain tissue potentializes their protective effects seemingly.

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Conflicts of interest

The authors declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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