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Histopathological effects of zingerone against lead acetate induced-brain dysfunction in rats

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Abstract

Compared with other organs, the nervous system is the most susceptible and a top target for lead-induced poisoning. At higher dosages, lead poisoning can be fatal or severely brain-damaging. This study aimed to explore the protective effect of zingerone on rats induced-brain oxidative stress by lead acetate on some pathological alteration. Using a random selection process, 40 male mature rats were allocated into four identical groups for the experiment and given the following care for 28 days: The control group (G1) was given distilled water, G2: gavage 16 mg/kg. B.W. of lead acetate, G3: 125 mg/kg. B.W. of zingerone and 16 mg/kg. B.W. of lead acetate, G4: 125 mg/kg. B.W. of zingerone. After collecting tissue from the brain samples, the cerebral cortex and hippocampus were separated for histological analysis. The result showed normal cerebral cortex and hippocampus histological architecture in the control group. The histology architecture of brain tissues in the lead acetate-treated group (G2) showed degeneration of neuronal cells, disruption of the cellular layers and atrophy, nuclear pyknosis, and neuronal injury. The G3 and G4 treated groups showed repair in the histological changes of the cerebral cortex and hippocampus due to zingerone's antioxidant and neuroprotective effects. Conclusion: Zingerone has antioxidant activity and neuroprotective properties by improving brain histological changes in rats.

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Introduction

Lead is a neurotoxicant with known behavioral and neurochemical effects, and it is a biological neurotoxin that has been shown to cause neuronal abnormalities even at minimal doses of exposure. Besides, the developing brain is especially vulnerable to Pb neurotoxicity, and exposure to it during this period has long-lasting adverse effects on the neuronal signaling, plasticity, and developmental trajectory of the brain (1,2). Because lead-treated rats' brains were homogenized, they had greater levels of lipid peroxidation and lower levels of reduced glutathione (GSH) and superoxide dismutase (SOD) activity (3,4). In humans and animals, the hippocampus is a crucial component of memory, learning, and spatial cognition (5). The cerebellum also controls motor coordination, balance, and smooth eye movements (6). The lead poisoning of the affected brain areas will influence the affected sections' form, function, and structure. It has been reported that lead toxicity causes neurological damage depending on several disorders, such as nerve damage, behavioral problems, mental retardation, Parkinson's disease, Alzheimer s disease, and schizophrenia (7,8). At the molecular level, lead can pass through the blood-brain barrier due to its ability to substitute for calcium ions via the interface of the regulatory action of calcium on the functions, which disrupts many intracellular biological activities (9,10). Lead might have a toxic effect through intrinsic and extrinsic induction of apoptotic pathways with

a prominent effect on brain tissue even at low doses (11). The environmental and occupational neurotoxicants after long-term exposure to lead are well known. The increase of lead levels in the hippocampus of adult rats exposed to lead from adolescence is characterized by an increase in malondialdehyde (MDA) and a decrease in GSH concentration and modulation of proteins related to neural physiology, hence a poor cognitive performance of short and long-term memories (12,13). Zingerone is a non-toxic, low-cost substance with a wide range of pharmacological effects. It is Zingiber officinale's least pungent ingredient (14,15). Zingerone is well recognized for its powerful pharmacological effects. Moreover, it is mainly found in dried ginger, but boiling or drying also causes the retro aldol reaction (a reaction in which a B-hydroxy carbonyl compound decomposes into an aldehyde or ketone, plus another carbonyl compound), which turns gingerol, another component of ginger, into zingerone (14,16). Numerous studies have shown that ginger benefits memory and has anti-neuroinflammatory properties that may help prevent and treat neurodegenerative illnesses (17). Additionally, ginger improves mouse cognitive function; however, subsequent studies in mouse hippocampi and rat C6 glioma cells demonstrated how the extract of ginger encouraged the development of synapses in the brain via the induction of extracellular signal-regulated kinase (ERK) produced by nerve growth factor (NGF) and cyclic AMP response element-binding protein (CREB) (18,19). Fermented ginger protected mouse hippocampal neuronal cells against amyloid 1-42 plaque-induced memory impairment in a mouse model of Alzheimer's disease (A.D.) and raised presynaptic and postsynaptic protein levels (19). The active component of ginger also demonstrated cellular protection against oxidative stress-related neuronal cell injury. It could efficiently scavenge different free radicals in PC12 cells (the cell line derived from rat pheochromocytoma is an immortalized cell line similar to the primary culture of fetal neurons) (20).

This study aimed to explore the protective effect of zingerone on rats induced-brain oxidative stress by lead acetate on some pathological alteration.

Materials and methods

Ethical approve

All experiences were approved by the ethical committee at the physiology, biochemistry and pharmacology departments at the faculty of veterinary medicine at the University of Baghdad, Iraq (ethical approval number: COVM-6361).

Methods

Forty adult male rats were randomly selected and treated for 28 days, weighing 190-220 gm., and housed in an animal house (College of Veterinary Medicine, Baghdad University). Animals were housed at 22 to 25 degrees Celsius with a 12-hour light/dark cycle. Throughout the study period, animals had unrestricted access to pellets and water. Following a 15-day acclimatization period, 40 male mature rats were allocated into four identical groups for the experiment. Groups were formed as follows: the G1 group gave distilled sterile water, G2 gavage orally 16 mg/kg. B.W. of lead acetate (PbAc), G3: 125 mg/kg. B.W. of zingerone and 16 mg/kg. B.W. of PbAc, orally, G4: 125 mg/kg. B.W. orally of zingerone (21). For a histological examination, after the withdrawal of blood, the head was cut and exited the brain from the skull, then the cerebral cortex and the production of the histological slices, the hippocampus were removed, blotted, opened longitudinally, and kept in 10% natural formalin buffer solution. Several tissue sections were prepared and stained with Hematoxylin-Eosin (H and E) stains according to the methods as described by Bancroft's (22).

Results

Histopathological examination

The G1 group showed normal histological architecture of the brain's cerebral cortex and normal neurons with normal superficial blood vessels (Figure 1). The cerebral cortex of G2 (PbAc): The main neural lesion showed variable-sized blood vessel congestion and dilation of the cerebral cortex with neural vacuolation and degeneration accompanied by focal cerebral gliosis. Other findings revealed shrinkage of neurons with eosinophilic cytoplasm and pyknotic nuclei together with central chromatolysis, the presence of multifocal necrotic lesions of cerebral parenchyma accompanied with few microglial infiltration, and meningeal vessels dilation with edema, mild leukocytic infiltration may record in other section (Figure 2). Histopathological changes in the cerebral cortex of G3-treated rats showed moderate dilation and congestion of cerebral vessels with scant leukocytic infiltration, and other sections showed moderate proliferation of microglial cells in the meningeal region with numerous capillary formations. Also, meningeal edematous findings with leukocytic infiltration accompanied by vascular congestion and dilation in parameter or (promoter) region indicate scattered neurons showed central chromatolysis may recorded with prominent perivascular edema and increased neuronal density. Also, there is moderate dilation of meningeal vessels associated with mild perivascular mononuclear cell cuffing (Figures 3). Histopathological sections of the cerebral cortex in the zingerone supplement treated group (G4) showed multifocal gliosis with few degenerated neurons with a large aggregation of neuroglia cells composed of oligodendrocytes, also focal proliferation of oligodendroglia in cerebral cortex tissue mainly in parameter region, mild dilation and congestion of meningeal vessels associated with mild perivascular MNCs infiltration (Figure 4).

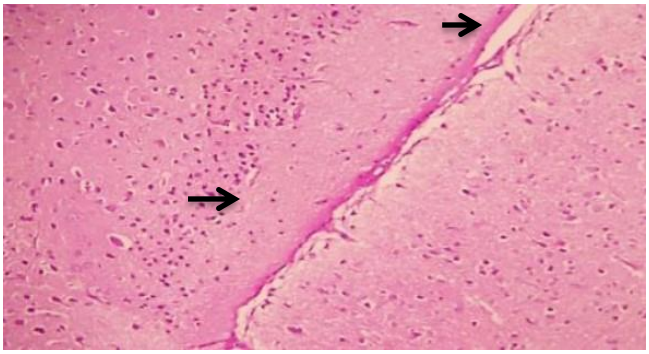

Figure 1: The histopathological section of the G1 group of cerebral cortices group showed normal neurons with normal superficial blood vessels (black arrow) (H & E stain 10x).

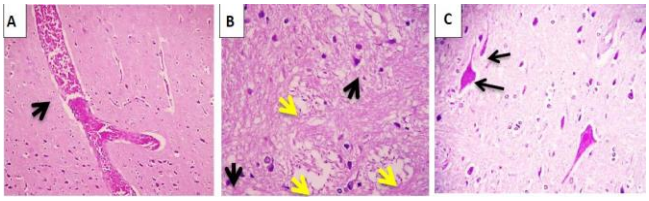

Figure 2: Histopathological section of the cerebral cortex of group G2 at 28 days post-treated orally with 16 mg/kg sublethal dose of PbAc. [A] shows blood vessel congestion and dilation (black arrow) of the cerebral cortex. [B] shows multifocal necrotic lesions (yellow arrow) of cerebral parenchyma accompanied by a few microglial infiltrations with neuron degeneration. [C] shows shrinkage (black arrow). H&E, 10x.

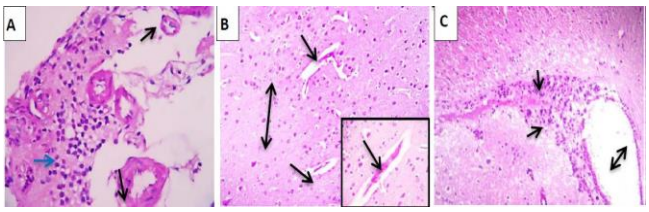

Figure 3: Histopathological section of the cerebral cortex of group G3 at 28 days post-treated orally with 16 mg/kg B.W. sublethal dose of PbAc and 125 mg/kg of zingerone supplement. [A] showed moderate proliferation of microglial (blue arrow) cells in the meningeal region with numerous capillaries formation (black arrow). [B] showed prominent perivascular edema (black arrow) and increased neuronal density (two head arrow). [C]: showed moderate dilation of meningeal vessels (two head arrow) associated with mild perivascular mononuclear cells cuffing (black arrow). H&E, 10x, 40x.

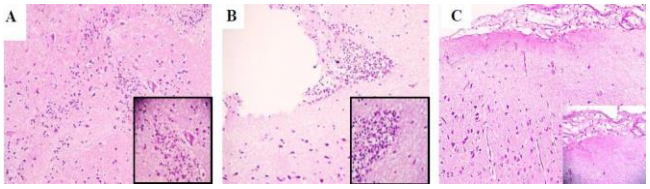

Figure 4: Histopathological section of the cerebral cortex of group G3 at 28 days post-treated with 125 mg/kg B.W. of zingerone supplement. [A] showed multifocal gliosis with few degenerated neurons. [B] showed multifocal gliosis with few degenerated neurons with a large aggregation of neuroglia cells composed of oligodendrocytes. [C]: showed focal proliferation of oligodendroglia in cerebral cortex tissue mainly in pia mater region, mild dilation and congestion of meningeal vessels associated with mild perivascular MNCs infiltration. H&E, 10x, 40x.

Brain hippocampus of the G1 group showed normal histological architecture of three layers: molecular (M), pyramidal (P), and polymorphic (Po) layers scattered presence of neuroglia cells and capillaries in both M and Po. Pyramidal cells comprise numerous compact layers of small P containing large vesicles, nuclei, and pale basophilic cytoplasm. Note: The normal pyramidal layer comprises packed rounded neurons containing large vesicular nuclei (Figure 5). The hippocampus showed that severe morphological changes were noticed in the hippocampus section of the G2 treated group after 28 days of (16 mg/kg B.W.) PbAc showed a marked decrease in cell density with the presence of degenerated dark pyramidal neurons. Also, disorganization loss of the structure of the pyramidal cell layer may recorded with massive vacuolation and nuclear pyknosis of neurons in the molecular layer and atrophy of the remaining pyramidal cells. At the same time, other advanced findings exhibit marked disruption of the pyramidal layer with no apparent distinction between molecular and Po layers (Figure 6). The hippocampus of G3-treated rats found slight neuronal degeneration with several shrunk pyramidal cells. The prominence of small pyramidal cells with vacuole formation was recorded in hippocampus tissues, mainly in pyramidal cells and adjacent Po, while not observed in the molecular layer. Other manifestations showed minimum neuronal changes, mainly in small pyramidal cells with apoptotic findings, while evidence of healthy neurons was detected in both molecular and Po layers (Figure 7). The findings of the hippocampus of group G4 (zengirone supplement) indicate fewer degeneration vacuolar findings were observed with less nuclear pyknosis, mainly in pyramidal and molecular neurons with moderate vacuolation of neurons in the Po layer. Also, focal neuroglial gliosis was reported in molecular cells. The other section showed large pyramidal neurons with degenerated axons accompanied by edematous-like substance presence (Figure 8).

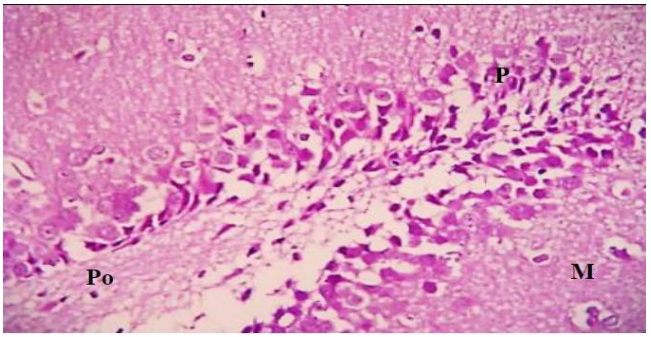

Figure 5: The histopathological section of the control group of hippocampi showed a normal pyramidal layer composed of packed rounded neurons containing large vesicular nuclei. M: molecular, P: pyramidal, Po: polymorphic. H&E, 40x.

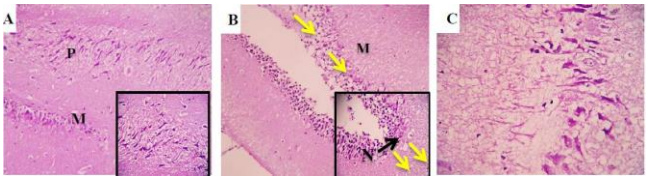

Figure 6: Histopathological section of the hippocampus of group G1 at 28 days post-treated with 16 mg/kg sublethal dose of lead acetate. [A] showed a marked decrease in cell density and degenerated dark pyramidal neurons (P) with massive atrophy and shrink of pyramidal cells (M). [B] shows that disorganization loss of the structure of the pyramidal cell layer may be recorded with massive vacuolation (yellow arrow) and nuclear pyknosis of neurons in the molecular layer of the remaining pyramidal cell (N) with scattered neuroglia (M). [C]: showed marked disruption of the pyramidal layer with no obvious distinction of molecular and Po layer. H&E, 10x, 40x.

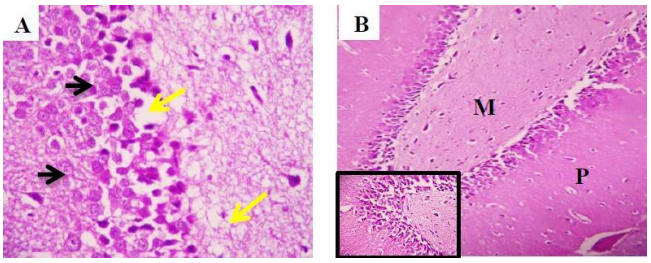

Figure 7: Histopathological section of the hippocampus of group G2 at 28 days post-treated with 16 mg/kg sublethal dose of lead acetate and 125 mg/kg of zingerone supplement. [A]: Histopathological section of Hippocampus of G2 treated rats finding prominence of small pyramidal cells (black arrow) with vacuole formation were recorded in hippocampus tissues (yellow arrow), and [B] showed no evident pathological changes. H&E, 10x, 40x.

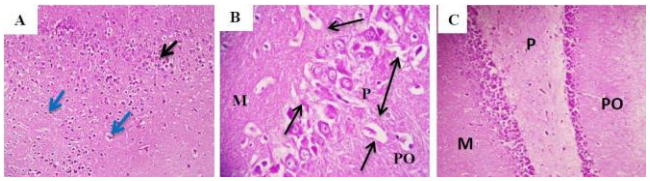

Figure 8: Histopathological section of the hippocampus of group G3 at 28 days post-treated with 125 mg/kg of zingerone supplement. [A] showed neuroglial gliosis mainly composed of oligodendrocytes and astrocytes (black arrow) was reported in molecular cells associated with numerous capillaries (blue arrow). [B] showed large pyramidal neurons with degenerated axons (two head arrow) accompanied with edematous like substance presence (black arrow). [C]: showed regular morphological changes of hippocampus layers with reduced number in small pyramidal cells. H&E, 10x.

Discussion

Histological examinations of the cerebral cortex and hippocampus in the current study showed normal histological architecture of the G1 group. The histology changes of brain tissues in G2 treated group observed in this study could be explained by the generation of ROS caused by lead exposure with depletion of antioxidant reserves; these results may be due to the ability of PbAc to pass through the blood-brain barrier due to its calcium ion substituting ability to damage the cerebral cortex and hippocampus (23). These findings align with Flora *et al.* (24), who reported that PbAc disrupts the brain barrier, allowing albumin to pass through the central nervous system tissues and causing a rise in intracranial pressure, edema, and neurodegeneration.

According to studies Sharifi *et al.* (25), administered PbAc to rats and mice caused an increase in the mRNA and protein levels of apoptotic factors, including caspase and Bcl-2 associated X protein (Bax), which led to an elevation in neurodegeneration (26). Other observations made in the current data, such as atrophy, nuclear pyknosis, and neuronal damage, are comparable to those made by scientists who studied acrylamide toxicity's effects on rat hippocampus neuronal cells (27-29). Inflammation and cell death are induced by the cellular byproducts of oxidative damage following PbAc treatment. These results agree with Liu *et al.* (30), who reported that exposure of young mice to lead-induced significant microgliosis and astrogliosis in the hippocampus by triggering Toll-like receptor 4 (TLR4)/ myeloid differentiation primary response 88 (MYD88)/ nuclear factor-(N.F.)-kB-signaling cascades. Following Khalaf *et al.* (31) and according to the results of the current study's extensive vacuolation, PbAc-treated rats had significant hippocampus cellular injury comparable to vacuolization and edema. A recent histopathological study

supported these morphological changes observed in the tissues (32,33).

Contrarily, PbAc and zingerone supplement (G3)-treated rats demonstrated an essential change in the altered histopathological structure and little neuronal alterations in the cerebellar cortex and hippocampus of G3 treated rats, slight neuronal degeneration with few numbers of shrunk pyramidal cells and prominence of small pyramidal cells with little vacuole formation. The antioxidant capabilities of zingerone may cause therapeutic benefits (34). The results, which agreed with Moradi *et al.* (35) and showed that ginger improved the histological features of the brain, suggested that it may have a neuroprotective effect. This effect is likely due to the polyphenolic compounds in ginger, which have the highest antioxidant and anti-inflammatory values of all-natural products that decrease neuronal damage by protecting the brain tissues against oxidative stress induced by PbAc. These results agree with Shen *et al.* (36), who reported that in rats, the application of ginger prevented demyelination, facilitated remyelination of the corpus callosum, and possessed management of neuronal damage in the cerebral cortex and hippocampus through the propagation of antioxidant capacity.

Farag *et al.* (37) suggests ginger supplementation reduced pain behaviors and possible blood-brain barrier breakdown. Furthermore, Badawy *et al.* (38) indicates that a significant neuroprotection of ginger was observed in rats by suppressing the astrocytes. As a result of ginger's ability to reduce cell death, restore motor function, and have neuroprotective effects in rats with spinal cord injuries, the brain tissues of the ZS-treated group showed structural repair (39,40). Dalsasso *et al.* and Mabrouk *et al.* (41,42) reported that gingerol (one component of ginger) may improve hippocampal levels of brain-derived neurotrophic factors and decrease apoptosis and oxidative DNA damage, which is likely how gold nanoparticle exposure increased nerve growth factor levels in rats.

Conclusion

The zingerone antioxidant activity and neuroprotective properties showed improved brain histological changes in rats against lead acetate.

Acknowledgment

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Conflict of interest

There is no conflict of interest.

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التأثيرات النسيجية المرضية للزنجرون ضد الخلل الوظيفي المستحدث بأسيتات الرصاص في الجرذان

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الخلاصة

على عكس الأعضاء الأخرى، يبدو أن الجهاز العصبي هو الأكثر عرضة والهدف الأكبر للتسمم المستحدث بالرصاص. في الجرعات العالية، يمكن أن يكون التسمم بالرصاص قاتلا أو ملحقا أضرار جسيمة بالدماغ. هدفت هذه الدراسة إلى الكشف عن التأثير الوقائي للزنجرون على الجرذان التي يسببها الإجهاد التأكسدي للدماغ بواسطة أسيتات الرصاص في بعض التغيرات الفسيولوجية المرضية. تم اختيار أربعين جرذ بالغا عشوائيا وقسمت بالتساوي إلى أربع مجموعات تجريبية وتمت معاملتها لمدة ٢٨ يوما على النحو التالي: أعطيت مجموعة السيطرة (المجموعة الأولى) ماء معقما مقطرا، المجموعة الثانية جرعت ١٦ ملغم / كغم من وزن الجسم من أسيتات الرصاص، المجموعة الثالثة جرعت ١٢٥ ملغم / كغم من وزن الجسم من الزنجرون و ١٦ ملغم / كغم من وزن الجسم. من أسيتات الرصاص، أما المجموعة الرابعة جرعت ١٢٥ ملغم / كغم من وزن الجسم من الزنجرون. تم جمع عينات أنسجة المخ ثم عزل قشرة المخيخ والحصين للفحص النسيجي. أظهرت نتائج التركيب النسـجي الطبيعي لقشرة الدماغ والحصين والتركيب النسـيجي للقشرة

الدماغية والحصين في المجموعة الأولى (السيطرة). أما في المجموعة الثانية فأظهرت تنكس الخلايا العصبية وتمزق الطبقات الخلوية وضمورها، والتضخم النووي وأذى الخلايا العصبية. بينما أظهرت المجموعتين الثالثة والرابعة إصلاحا في التغيرات النسيجية للقشرة الدماغية والحصين بسبب التأثير المضاد للأكسدة والوقاية العصبية لمادة الزنجرون. نستنتج أن الزنجرون له نشاط مضاد للأكسدة وخصائص وقائية للأعصاب عن طريق تحسين التغيرات النسيجية للمخ في الفئران.