Ameliorative effect of selenium nanoparticles and ferulic acid on acrylamide-induced neurotoxicity in rats

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ABSTRACT

Objective: In the present study, the effect of selenium nanoparticles (SeNPs) and ferulic acid (FA) on acrylamide (AC) induced neurotoxicity in rats was investigated.

Methods: Sixty adult male rats were divided equally into six groups and orally treated as follows: Group I (control): 1ml per day physiological saline; group II (SeNPs): 0.5 mg/kg body weight per day SeNPs for 21 days; group III (FA): 100 mg/kg body weight per day FA for 21 days; group IV (AC): 50 mg/kg body weight per day acrylamide for 21 days; group V (AC+SeNPs): AC 50 mg/kg body weight for 21 days then SeNPs as group II. Group VI (AC+ FA): AC 50 mg/kg body weight per day then FA as group III.

Results: AC significantly ($P<0.05$) increased the level of β-amyloid (Aβ) in brain tissue and interleukin 6 (IL-6) in serum and significantly ($P<0.05$) decreased the level of Brain-Derived Neurotrophic factor (BDNF) in the brain tissue compared to control group.

Treatment with FA or SeNPs significantly ($P<0.05$) decreased the level of Aβ in brain tissue and IL- 6 in serum and significantly ($P<0.05$) increased the level of BNDF in brain tissue compared to acrylamide group.

AC induced histopathological changes in brain hippocampus and striatum which were improved with SeNPs and FA treatment.

Conclusion: It is concluded from the present study that ferulic acid and SeNPs had a therapeutic effect against neurotoxicity induced by AC in experimental rats.

KEY WORDS: Acrylamide neurotoxicity
Ferulic acid
Selenium nanoparticles

Introduction

Acrylamide (AC) is a low molecular weight vinylic compound. It is highly soluble in water, easily reactive in air and rapidly polymerizable. It is present in cooked foods and cigarette smoke. AC is considered as one of the main contaminants formed in potato, cereals and bakery products, during the heat treatment of foods [1]. Water is one of the major sources of exposure as polyacrylamide is used mainly for the purification of drinking water as a flocculating agent. AC is also found in cocoa powder, and roasted almonds. Coffee drinking and smoking are other major sources of exposure [2]. AC is not a substance that is added to food, but it is formed in food during heat processing. AC formation follows different routes in conjunction with the Maillard reactions system in food products, where the asparagine route is the major one for the formation of AC [1]. The low molecular weight and high water solubility of AC enable this compound to easily pass through various biological membranes [3]. Subsequently, the characteristic chemical structure of AC and its ability to undergo metabolic transformation make it reacts with different (sub) cellular targets. AC can also bind to plasma proteins, primarily Hb, with an, as of yet, undefined biological consequence. Hb-bound AC is essentially considered as the internal dose marker of exposure to AC.

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Furthermore, AC can undergo oxidative biotransformation by cytochrome P450 2E1 (CYP2E1) [4]. The resulting metabolite is an epoxide derivative, i.e. glycidamide, which is more reactive toward DNA and proteins than the parent compound, AC [3]. AC is a well-recognized potent neurotoxin affecting both the central nervous system (CNS) and peripheral nervous system (PNS). Only the AC monomer is toxic while AC polymers are non-toxic [5]. Neurotoxicity

is characterized by ataxia, skeletal muscle weakness, and numbness of the hands and feet produced by the sub-chronic, low-level occupational exposure of humans to AC [6]. Experimental AC intoxication was associated with neurogenic autonomic dysfunction, e.g. urinary retention, baroreceptor dysfunction, and impaired vasomotor control [7]. The mechanism underlying neurotoxicity by AC is the subject of debate. The morphological hallmark of this toxic neuropathy was considered to be distal preterminal axon swellings of the longest myelinated fibers. These swellings contained an abundance of neurofilaments, tubulo-vesicular profiles and probably degenerating mitochondria [8]. There are three important hypothesis considering AC neurotoxicity: inhibition of kinesin-based fast axonal transport, alteration of neurotransmitter levels, and direct inhibition of neurotransmission. [9]. AC binds to and inhibits the motor protein kinesin, leading to the inhibition of the anterograde and retrograde transport. Also AC could affect the cellular energy generation and the deficiency of energy induced the neurotoxicity. On the other hand, oxidative stress has been demonstrated to be one of the key mechanisms in many chemical-induced cell injuries. Oxidative stress in the cells and tissues refers to enhance generation of reactive oxygen species (ROS) and/or depletion of antioxidant defense system, causing an imbalance between prooxidants and antioxidants, potentially leading to damage. ROS can attack the polyunsaturated fatty acid in the biomembrane and induce free radical chain reactions, leading to the enhancement of lipid peroxidation. Oxidative stress can result in a number of pathological conditions such as Alzheimer's disease (AD), Parkinson's disease (PD) atherosclerosis, cancer and diabetes. AC decreased glutathione (GSH) content and anti-ROS activity in the brain. GSH depletion and lipid peroxidation are considered as primary events in the AC induced neuropathy [10]. Ferulic acid (FA) (4-hydroxy-3-methoxycinnamic acid) is a widely plants constitute. It is most abundant in cereal grains where FA can reach the concentration of 2 g/kg dry weight. FA belongs to a widely class of phenols in particular to the hydroxylcinnamic acids [11]. *In vivo* FA converted into a variety of metabolites such as ferulic acid-sulfate, ferulic acid-glucuronide, ferulic acid-sulfoglucuronide (major metabolites in the plasma and urine of rats), ferulic acid-diglucuronide, feruloylglycine, m-hydroxyphenylpropionic acid, dihydroferulic acid, vanillic acid and vanilloylglycine. It was reported that the major pathway of FA metabolism is the conjugation with glucuronic acid and/or sulfate which occurs mainly in the liver by the action of sulfotransferases and uridine diphosphate (UDP) glucuronosyl transferases. On the other hand, small amount of conjugation reaction takes place in intestinal mucosa and kidney. Also, a small amount of FA possibly metabolized in the liver through β oxidation [12]. FA exhibits a wide range of biochemical application including antioxidant, antiallergic, hepatoprotective, anticarcinogenic, anti- inflammatory, antimicrobial, antiviral, vasodilatory effect, antithrombotic, and helps to increase the viability of sperms [13]. FA is considered as a powerful hunter of ROS and reactive nitrogen species (RNS) which, generated in the brain,lead to protein, DNA and RNA oxidation and lipid peroxidation [14]. Neurodegenerative diseases such as AD and PD which are associated with chronic inflammation and formation of oxidation stress resulting from ROS and RNS affect essential proteins, damage DNA, RNA and produce lipid peroxidation which leads to neural dysfunction [15]. Due to the anti-inflamatory and antioxidant properties of FA, it plays an important role in the treatment and protection against AD [16]. FA inhibits the formation of Aβ plaques and fibrils so it could prevent the development of AD, not only through scavenging ROS but also through the direct inhibition of the deposition of fibrils in the brain [17]. Selenium (Se) is a semi metal and it consequently possesses intermediate properties between a metal and a non-metal [18]. It is present in nature and in organisms as organic and/or inorganic forms. The main organic forms are selenomethionine (Semet) and selenocysteine (Secys). The inorganic forms are selenite (SeO_3^{-2}), selenide (Se^{2-}), selenate (SeO_4^{-2}) and the Se element [19]. The best metabolic pathway of Se compounds delivered from food is the reduction of selenites to selenide H_2Se and then its methylation to form trimethylselenonium ions [$(CH_3)_3Se^+$]. The selenide acts as active Se in the synthesis of selenoproteins [20]. The formation of selenoproteins from Se plays many important roles in many biological functions such as antioxidant defense, formation of thyroid hormones, DNA synthesis, fertility and reproduction [18].

Se deficiency associates with lower cognitive function and damaged motor function [21]. Several studies indicate that patients with AD and PD have a low level of Se and this may be due to the role of Se in the formation of selenoprotein in the brain inhibiting further oxidative damage [22].

Materials and Methods

Chemicals

Acrylamide dry crystals (C_3H_5NO, > 99% purity) was obtained from sigma chemicals Co, USA. Ferulic acid ($C_{10}H_{10}O_4$, Molar mass: 194.18 g/mol) was brought from Acros Organics CO, USA. Selenium dioxide (SeO_2, Molecular weight: 110.96 was obtained from Sigma-Aldrich, part of Merck Company, USA. Ginger (*Zingiber officinale* rhizome dried roots was purchased from the local market, and grinded to a powder).

Ginger extraction preparation

The extract of *Zingiber officinale* rhizome dried roots extract was used to prepare selenium nanoparticles. About 20 gm of *Z. officinale* rhizome dried roots powder was immersed in a beaker containing 200 mL double distilled water and boiled for 30 min. The extract was cooled down and filtered with Whatman filter paper no.1 and the extract was stored at 4 °C [23].

Selenium nanoparticles preparation (SeNPs)

The aqueous extract of ginger obtained was used as a precursor for synthesis of SeNPs. Ginger extract (2 ml) was added drop wise into the 20 ml solution of SeO_3 (10 mM), with vigorous stirring. The mixture was incubated by placing the solution onto a rotatory orbital shaker operating at 200 rpm, 30 °C for 72 h in dark conditions. The reduction of selenium ions was monitored by sampling an aliquot (3 ml) of the mixture at intervals of 24 h, followed by measurement of absorption maximum. Absorption maximum was determined by measuring optical density of the content from wavelength 350 to 700 nm using UV–Vis spectrophotometer [24].

Ferulic acid preparation

FA was dissolved in sterile water and oral administrated at a dose of 100 mg/kg body weight.

Experimental animals

Sixty Swiss Albino male rats (150-200 g) were drawn from animal house of The Nile Company for Pharmaceuticals & Chemical Industries, Cairo, Egypt. They were maintained on a standard pellet diet and tap water. The animals were housed in suitable cages in conditioned atmosphere (20-22 °C) and they were allowed 7 days for adaptation.

Experimental design

Rats were divided into six groups (10 rats each):

Group 1 (control): Animals were administrated orally by gavage 1 ml of physiological saline.

Group 2 (SeNPs): Rats were administrated orally by gavage SeNPs (0.5 mg/kg body weight per day) for 21 days.

Group 3 (FA): Rats were administrated orally by gavage FA (100 mg/kg body weight per day) for 21 days.

Group 4 (AC): Rats were administrated orally by gavage with AC (50 mg/kg body weight per day) for 21 days.

Group 5 (AC+SeNPs): Rats were received AC as group 4 and then SeNPs as group 2.

Group 6 (AC+FA): Rats were received AC as group 4 and then FA as group 3.

Blood samples

At the end of the experiment, rats were scarified and blood samples were collected by heart puncture. Serum of each sample was collected by centrifugation at 3000 rpm for 10 min.

Brain tissues

Brain tissue of experimental animals were dissected and divided into two parts, one part was kept in 10% formaline for histopathological studies and the other part was homogenized (10% w/v) in phosphate-buffered-saline (0.2 M sodium phosphate buffer with 0.15 M sodium chloride, pH 7.4) in a glass tissue homogenizer with Teflon pestle.

Determination of brain derived neurotrophic factor (BDNF) in brain tissue

BDNF was determined in the brain tissue homogenate using the kit supplied by Boster Biological Technology, Rat BDNF Picokin^{TM} ELISA kit.

Determination of amyloid beta peptide 1-42 (Aβ 1-42) in brain tissue

Aβ 1-42 was determined in the brain tissue homogenate using the kit supplied by My Biosource, Rat amyloid beta peptide 1-42 (Aβ1-42) ELISA Kit.

Determination of Interleukin 6 in plasma

The level of (IL- 6) was determined in the plasma using enzyme-linked immunosorbent assay (ELISA) kit (Ray Bio® Rat IL-6 ELISA kit).

Histopathological findings

Autopsy samples were taken from the rat brain tissue of different groups and fixed in 10% formalin for twenty-four hours. Washed with tap water then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56 degrees in a hot air oven for twenty-four hours. Paraffin bees wax tissue blocks were prepared for sectioning at a thickness of 4 microns by sledge microtome. The obtained tissue sections were collected on glass slides, deparaffinized, and stained by hematoxylin &eosin stain for examination through the light electric microscope [25].

Statistical analysis

SPSS version 20 was used for the statistical analysis. The data obtained were calculated by one- way analysis of variance (ANOVA). Difference were considered statistically significant at $P< 0.05$.

Results

Brain derived Neurotrophic factor (BDNF) in the brain tissue

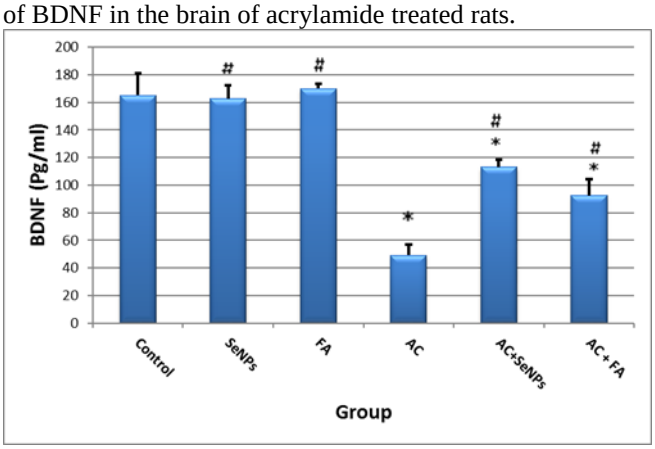
BDNF level (Pg/ml) was determined in the brain tissue and results were represented in (table,1) and (figure 1).

Table 1. Effect of SeNPs and ferulic acid on BDNF level in the brain of acrylamide treated rats.

	Control Mean±SD	SeNPs Mean±SD	FA Mean±SD	AC Mean±SD	AC+SeNPs Mean±SD	AC + FA Mean±SD
BDNF (Pg/ml)	165.17±15.94	162.57±9.73	169.92±3.74	49.12±8.06[a]	113.00±5.26[a,b]	92.40±11.66[a,b]

a: significantly (P< 0.05) different from the corresponding control group
b: significantly(P< 0.05) different from the corresponding acrylamide group

Figure 1. The effect of SeNPs and ferulic acid on the levels of BDNF in the brain of acrylamide treated rats.



*, statistically significant difference vs. Control group.
#, statistically significant difference vs. Acrylamide group.

AC administration significantly (P<0.05) decreased BDNF in the tested brain tissue in comparison to control group (control; 165.17±15.94, AC; 49.12±8.06). On the other hand BNDF level was significantly (P<0.05) increased in AC groups treated with SeNPs (AC+SeNPs) or FA (AC+FA) compared to AC group (AC; 49.12±8.06, AC+SeNPs; 113.00±5.26, AC+FA; 92.40±11.66).

II. β-Amyloid in the brain tissue

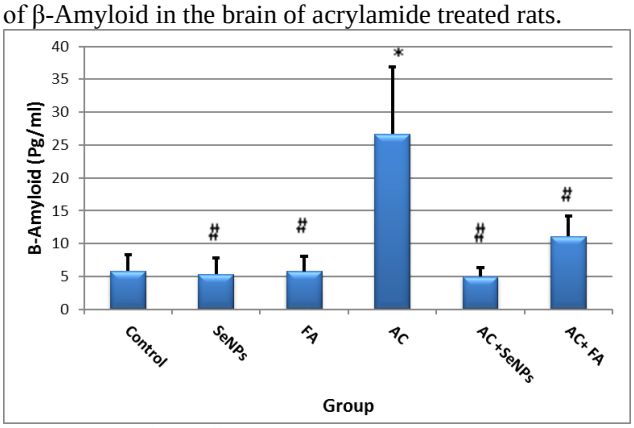
Aβ level (Pg/ml) was determined in the brain tissue and results were represented in (table, 2) and (fig. 2). Results showed that Aβ level was significantly increased (P< 0.05) in AC group compared to control (control; 5.83±2.47, AC; 26.67±10.18). Different treatments significantly reduced Aβ level. It was significantly decreased (P< 0.05) in AC groups treated with SeNPs (AC + SeNPs) or FA (AC + FA) compared to AC group (AC; 26.67±10.18, AC+SeNPs; 4.97±1.33, AC+FA; 11.10±3.08).

Table 2. Effect of SeNPs and ferulic acid on β-Amyloid level in the brain of acrylamide treated rats.

	Control Mean±SD	SeNPs Mean±SD	FA Mean±SD	AC Mean±SD	AC+SeNPs Mean±SD	AC + FA Mean±SD
β-Amyloid (Pg/ml)	5.83±2.47	5.33±2.47	5.76±2.35	26.67±10.18[a]	4.97±1.33[b]	11.10±3.08[b]

a: significantly (P< 0.05) different from the corresponding control group
b: significantly(P< 0.05) different from the corresponding acrylamide group

Figure 2. The effect of SeNPs and ferulic acid on the levels of β-Amyloid in the brain of acrylamide treated rats.



*, statistically significant difference vs. Control group.
#, statistically significant difference vs. Acrylamide group.

III. Interleukin-6 (IL-6) in serum

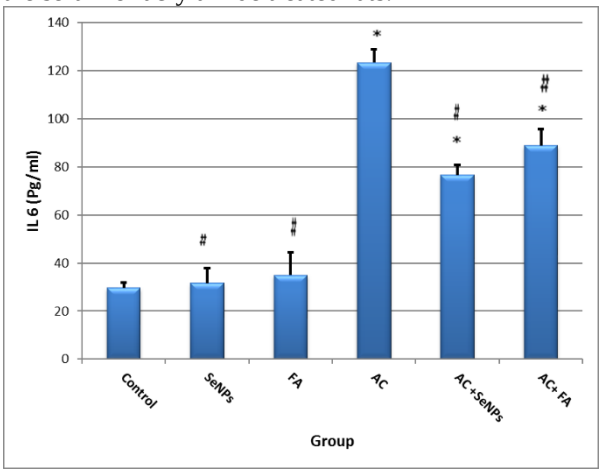
IL-6 level (Pg/ml) was determined in the serum and results were represented in (table, 3) and (figure 3). Results showed that IL-6 level was significantly increased (P< 0.05) in AC group compared to control group (control; 29.60±2.34, AC; 123.38±5.63). On the other hand IL-6 level was significantly decreased (P< 0.05) in AC groups treated with SeNPs (AC + SeNPs) or FA (AC + FA) in compared to AC group (AC; 123.38±5.63, AC+SeNPs; 76.50±4.42, AC+FA; 88.87±6.76) .

Table 3. Effect of SeNPs and ferulic acid on IL-6 level in the serum of acrylamide treated rats.

	Control Mean±SD	SeNPs Mean±SD	FA Mean±SD	AC Mean±SD	AC+SeNPs Mean±SD	AC + FA Mean±SD
IL 6 (Pg/ml)	29.60±2.34	31.68±6.25	34.95±9.49	123.38±5.63[a]	76.50±4.42[a,b]	88.87±6.76[a,b]

a: significantly (P< 0.05) different from the corresponding control group
b: significantly(P< 0.05) different from the corresponding acrylamide group

Figure 3. Effect of SeNPs and ferulic acid on IL-6 level in the serum of acrylamide treated rats.



*, statistically significant difference vs. Control group.
#, statistically significant difference vs. Acrylamide group.

Histopathological findings

Histopathological changes in the control, SeNPs and FA groups brain corpus striatum showing no histological changes with normal neuclei, normal blood capillaries and slight neuroglial cells. AC intoxicated group showing excess degenerative plaques, necrosis and apoptosis in neuronal cells, dilated blood capillaries and infiltration by excess neuroglial cells. AC + SeNPs group and AC + FA group showing less degenerative changes, less necrosis and apoptotic in neuronal cells but excess infiltration by neuroglial cells and newly formed dilated capillaries with glaiosis. Large focal nodules of neuroglial cells and glaiosis are clearly seen in AC + FA group (figure 4.). The semi-quantitative histopathological changes of the brain striatum are shown in (table 4). Histopathological changes in the brain hippocampus showing normal neuronal cells and normal blood capillaries in control group, SeNPs group and FA group while, AC intoxicated group showing massive palisading necrosis, marked apoptosis and marked increase in neuroglial cells infiltration.

Table 4. The histopathological changes in the brain striatum of the different groups.

Groups Pathological feature	Control group	SeNPs group	FA group	AC group	AC+SeNPS group	AC+FA group
Neuronal cells	Normal	Normal	Normal	Excess degenerative changes (+++)	Slight degenerative changes (+)	Slight degenerative changes (+)
Neuroglial cells	+	+	+	+++	++	+++
Blood capillaries	Normal +	Normal +	Normal +	New dilated capillaries (++)	New dilated capillaries (++)	New dilated capillaries (++)
Degenerative plaques	----	----	----	+++	+/-	++
Necrosis	----	----	----	+++	+	++
Apoptosis	----	----	----	++	+	++
Neuroglial cell nodules	----	----	----	----	----	++
Glaiosis	----	----	----	----	+	++

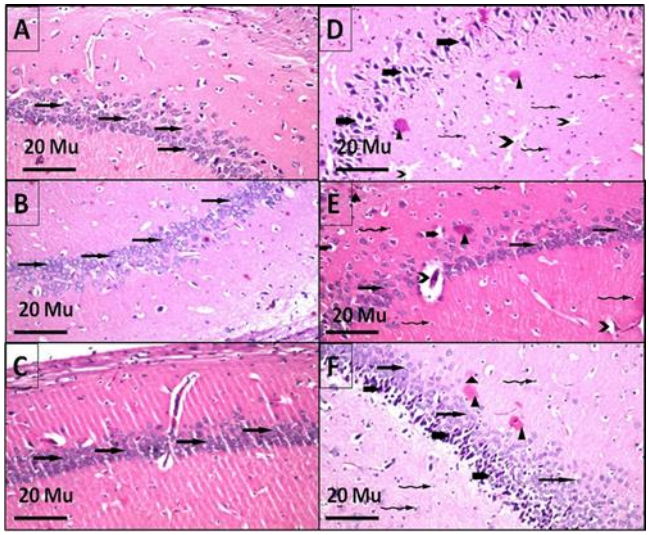


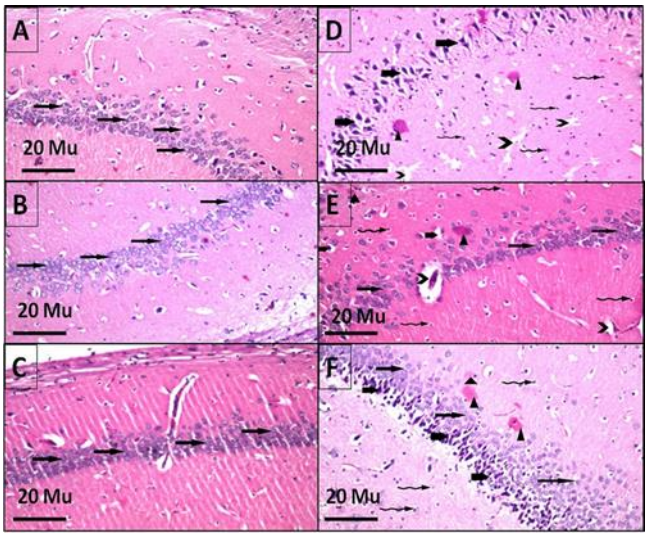
Figure 4. Histopathological changes in the brain corpus striatum showing no histological changes with the normal neuronal neuclei (black arrows), normal blood capillaries (arrow heads) and slight neuroglial cells infiltration (wavy arrows) in (A) control group, (B) SeNPs group and (C) FA group. (D) AC intoxicated group showing excess degenerative plaques (black arrow), necrosis and apoptosis (triangles) in neuronal cells, dilated blood capillaries (arrow heads) and infiltration by excess neuroglial cells (wavy arrows). (E) AC + SeNPs group and (F) AC + FA group showing less degenerative changes and less necrosis and apoptotic (triangles) in neuronal cells but excess infiltration by neuroglial cells (wavy arrows) and newly formed dilated capillaries (arrow heads) with glaiosis (asterisk). Large focal nodules of neuroglial cells and glaiosis (wavy arrows and asterisk) are clearly seen in AC + FA group.

Table 5. showing the histopathological changes in the brain hippocampus of the different groups.

Groups Pathological feature	Control group	SeNPs group	FA group	AC group	AC+SeNPS group	AC+FA group
Neuronal cells	Normal	Normal	Normal	massive necrosis (+++)	Slight degenerative (+)	marked necrosis (++)
Neuroglial cells	Normal	Normal	Normal	Marked infiltration (+++)	Slight infiltration (+)	Marked infiltration (+++)
Blood capillaries	Normal	Normal	Normal	dilated (++)	slight dilated (+)	dilated (++)
Palisading Necrosis	----	----	----	Massive +++	Slight +	Marked ++
Apoptosis	----	----	----	Marked ++	Slight +	Marked ++

AC+SeNPs groups showing slight degenerative changes in neuronal cells, slight apoptosis, infiltration by neurogalial cells and slight increase blood capillaries. AC+FA group showing marked palisading necrosis in the lower third of the neuronal cells with marked apoptosis and infiltration by neuroglial cells (figure 5.). The semi-quantitative histopathological changes of the brain hippocampus are shown in (table 5).

Figure 5. Histopathological changes in the brain hippocampus showing normal neuronal cells (thin arrows) and normal blood capillaries in (A) control group, (B) SeNPs group and (C) FA group. (D) AC intoxicated group showing massive palisading necrosis (thick arrows), marked apoptosis (triangle), marked increase in neuroglial cells (wavy arrows) and blood capillaries (arrow heads). (E) AC + SeNPs groups showing slight degenerative changes in neuronal cells (thick arrows), slight apoptosis (triangle), infiltration by neurogalial cells (wavy arrows) and slight blood capillaries (arrow heads). (F) AC+FA group showing marked palisading necrosis (thick arrows) in the lower third of the neuronal cells (thin arrows) with marked apoptosis (triangle) and infiltration by neuroglial cells (wavy heads).



Discussion

In Industrial and laboratory uses, it has been reported that the formation of AC is associated with high-temperature (higher than 200°C) cooking processes in certain carbohydrate-rich foods, especially when asparagine react with sugar [26]. Dietary AC intake may increase the risks of kidney and breast cancer [27] and tests on animals prove that AC has genotoxic and neurotoxic effects, causing gene mutation and DNA damage, and it may represent a health hazard for humans [28]. AC is a well documented neurotoxicant in both humans and laboratory animals. Subchronic, low-level occupational exposure of humans to AC produces neurotoxicity characterized by ataxia, skeletal muscle weakness and numbness of the hands and feet [29]. The present study, demonstrated the neurotoxicity effect of AC on some biochemical parameters such as (BDNF, A β and IL- 6) and also in the histological changes in the brain of the experimental animals. The result of the current study showed that oral exposure to AC (50 mg / kg for 21 days) induced neurotoxicity in rats.

BDNF is one of the neurotrophic factors which are an extremely important brain development factor that maintains neuron growth, synaptic functions, and neural plasticity. BDNF supports the development of noradrenergic and serotonergic neurons and protects them from toxic damages. It regulates neuronal continuity and plasticity with its positive effect on dendrite growth. The present results showed declined activity of brain BDNF in AC treated rats. This may be due to the oxidative stress of AC in the brain tissue. In accordance, several studies indicated that AC induced significant decrease in brain BDNF in rats. [30, 31].

Aβ peptide is an important risk factor and has a central role in the onset and progression of AD. Aβ is produced in normal individuals but, under certain circumstances, this molecule may aggregate and start disease progression. There is strong evidence emphasizing that Aβ oligomers play the main role in neuronal dysfunction and AD [32]. The present study also indicated that exposure to AC leads to significant increase in the level of brain Aβ. This is due to acute disruption of transthyretin secretion by AC. Transthyretin serves as a thyroxine transport and is involved in Aβ peptide chelation attenuating neurotoxicity. The decrease in transthyretin levels induced by AC might be involved in neurotoxicity by affecting nerve regeneration as it shown in many previous studies [33- 35]. IL-6 is a cytokine originally identified almost 30 years ago as a B-cell differentiation factor, capable of inducing the maturation of B cells into antibody-producing cells. As with many other cytokines, it was soon realized that IL-6 was not a factor only involved in the immune response, but with many critical roles in major physiological systems including the nervous system. IL-6 is now known to participate in neurogenesis (influencing both neurons and glial cells), and in the response of mature neurons and glial cells in normal conditions and following a wide range of injury models. Its expression is affected in several of the main brain diseases, and animal models strongly suggest that IL-6 could have a role in the observed neuropathology and that therefore it is a clear target of strategic therapies [36]. The present study showed that AC significantly increased the level of IL-6 and is in agreement with a previous study [37]. AC exposure markedly decreased the glutathione (GSH), the depletion of GSH may make the nerve tissue more sensitive to

the oxidative stress in experimental animals [10]. The oxidative stress and over production of ROS due to AC neurotoxicity increase the inflammation in the nerve tissue which leads to over production of IL-6. FA is a natural compound that has phenolic group in its chemical structure. Health benefits of phenolic compounds such as FA attract the attention of many researches because of their antioxidant potentials [38]. In addition to its antioxidant properties, FA also has anti-carcinogenic, hepatoprotective, anti-inflammatory, anti-mutagenic and neuroprotective properties [39]. The present study showed the therapeutic effect of FA on AC induced neurotoxicity in experimental animals. Treatment with FA significantly increased the level of BDNF due to anti-depressive effect of FA. Several previous studies showed the anti-depressant-like effect of FA which minimises the depression resulted from oxidative stress of AC [40-42].

Also, treatment with FA significantly decreased the level of Aβ. FA is a phytochemical which exhibits both antioxidant and anti-inflammatory properties that may be of interest in the therapy of AD. Long-term, low dose FA administration via drinking water induces a resistance of the brain's toxicity to Aβ exposure [43]. Similarly, Kim et al. [44] demonstrated that long term administration of FA effectively protects against Aβ toxicity by inhibiting microglial activation *in vivo*. Another study by Sultan et al. [45] showed that FA significantly exerted protective effects against Aβ by modulating oxidative stress directly and by inducing protective genes in hippocampal culture. Finally, Ono et al. [46] showed that FA prevented the development of AD not only through scavenging ROS, but also through directly inhibiting the deposition of Aβ in the brain.

The present study showed that FA treatment decreased the level of IL-6 in the AC intoxicated animals. AC induces oxidative stress and increases the level of ROS and decreases the level of GSH, which lead to the overproduction of inflammatory substances such as IL-6. FA acts as anti-inflammatory agent that helps in decreasing the inflammation and IL-6 production. Many studies demonstrated the anti-inflammatory effect of FA on IL-6 level [47, 48].

Se is a trace element which is found in small amounts in the organism. The formation of selenoproteins from Se plays many important roles in many biological functions such as antioxidant defense, formation of thyroid hormones, DNA synthesis, fertility and reproduction. Also, Se can be transformed in the organism into different metabolites. Some, like methylselenol, play a role in cancer prevention. Se also has a role, besides vitamin E, in muscle function by improving endurance and recovery and slowing the ageing process. The present study showed that the therapeutic effect of SeNPs in AC induced neurotoxicity in experimental animals.

The present study showed the treatment with SeNPs increased the level of BDNF compared with AC intoxicated group. Se is a cofactor for many antioxidant enzymes such as glutathione peroxidase and thioredoxin reductase [49], it decreases the oxidative stress and helps in the scavenging of ROS from the brain tissue, as it helps to increase the levels of BDNF. Previous studies indicated the relation between the oxidative stress and the reduction in BDNF level in the experimental animals [50, 51].

The present study also showed that SeNPs also decreased the level of Aβ in the AC intoxicated group and this may be due to the antioxidant and anti-inflammatory effect of SeNPs and this agreed with a previous study [52]. Other studies suggested interaction between Selenoprotein P and Aβ, leading to complex formation. Also Aβ is strong metal chelator, binding for instance Cu and Fe [53-55].The accumulation of Cu and Fe appears to promote the progression of the Aβ cascade [56]. Ternary complexes can be formed between metal cations, Aβ and selenoproteins and such complexes are presumably less toxic than Aβ-metal complexes alone.

On the other hand, SeNPs decreased the level of IL-6 in the AC intoxicated group and this is due to the anti-inflamatory and antioxidant effects of Se. As many previous studies have indicated the anti-inflammatory effects of Se on IL-6 [57-59].

In the present study exposure to AC caused marked histopathological alternation in the brain tissues which were represented by excess degenerative plaques, necrosis, apoptosis and dilated blood capillaries in brain striatum and hippocampus. These results could be explained by the over production of ROS and oxidative stress related to AC effects on the brain tissue. These findings are in agreement with those reported by many investigators [60-63].

The histopathological results of FA treated AC intoxicated group showed marked palisading necrosis and apoptosis in hippocampus and slightly decreased in the degenerative plagues, necrosis and apoptosis in striatum. These results could be attributed to the therapeutic effect of FA against

the AC neurotoxicity. This may be due to the antioxidant properties of FA in scavenging the ROS and decreasing the oxidative stress as previously reported [64,65]

Also, the histopathological results show the role of SeNPs in minimizing the toxic effect of AC in the brain tissue. The SeNPs treated group showed less degenerative changes and less necrosis and apoptosis in striatum and hippocampus. SeNPs significantly reduced the brain tissue damage via suppression of oxidative stress and Scavenging of ROS as previously reported [66,67].

This study has shown that the FA and SeNPs have significant neuro therapeutic effect and significant decrease the neurotoxicity induced by AC in some biochemistry and histopathology of brain tissue. From biochemical and histological view, it is clearly that SeNPs has potent therapeutic activity in comparison with FA.

Conflict of Interest

We declare that we have no conflict of interest.

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