RESEARCH ARTICLE

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NEUROPROTECTIVE EFFECTS OF GINGER AGAINST SERTRALINE AS ANTIDEPRESSANT DRUG-INDUCED LESIONS IN SPINAL CORD OF MICE

ABSTRACT:

Sertraline is an antidepressant drug used for treatment of depression. However, there are several side effects occurred during its use in treatment. Ginger is a natural substance which has many biological effective roles such as immunomodulatory, antioxidant, and free radical scavenging and anti-inflammatory agent. The study was designed to clarify the histological, ultrastructural and immunohistochemical alterations in the spinal cord of male albino mice after ingestion of sertraline and to elucidate of the protective role of ginger extract against the side effects of this antidepressant drug. Forty adult male albino Wister mice were divided into four groups ; group 1 ingested distilled water , group 2 ingested 50 mg/l (10%) ginger extract, group 3 ingested sertraline (0.13 mg/kg/BW), group 4 ingested sertraline and then was given ginger extract after 1 hour. All groups were treated for 28 consecutive days. The animals were sacrificed and the cervical region of the spinal cord from each animal was taken and processed for both light and electron microscopic examinations. Histopathological and ultrastructural studies revealed significant alterations in the motor and sensory neurons of the spinal cord after treatment with sertraline. These changes were confirmed by the immunohistochemical expression results. Sections of animals treated with sertraline followed by ginger revealed marked ameliorative effects. It is concluded that ginger has a protective effect by avoiding the side effects of the sertraline.

KEY WORDS:

Sertraline, ginger, spinal cord, immunohistochemstry, Ultrastructure

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INTRODUCTION:

Selective serotonin reuptake inhibitors (SSRIs) are drugs used for many purposes such as major depression, panic disorder, obsessive compulsive disorder and sometimes for obesity, post-traumatic stress disorder, social phobia and premenstrual disorder. Recently, the new generation of the SSRIs was used on the wide scale all around the world (Stanford, 1999; Sadock *et al*., 2009).

In comparison to other types of antidepressants, SSRIs have less adverse effects with nausea, diarrhea, sexual dysfunction, headache, dizziness, agitation, insomnia but under certain circumstances increased suicide risk (Vaswani *et al*., 2003). The mechanism of action involves the inhibition of serotonin (5-HT) reuptake into pre-synaptic nerve endings which allows higher serotonin levels in the synaptic cleft (Hyman *et al.*, 1996).

Also, Knutson *et al.* (1998), Serra *et al.* (2006), Tang *et al.* (2009), and Simmons and Allen (2011) recorded that the experimental manipulation of 5-HT level in healthy human adults influences the mood and personality in the absence of clinical disorder. Furthermore there are two mechanisms by which SSRIs may achieve clinical effect (at least for mood disorders) by changing mood and/or personality processes.

Moreover, it was found that there are many side effects for the SSRIs drugs uses. Various side effects and experimental indications were reported from in vitro animal studies (Brandes and Hogg, 1992; Taler *et al.*, 2007). In addition, the patients suffering from depression which are treated with SSRIs could result in some cellular immune response whereas cytokine levels were shown

to be markedly reduced following the administration of SSRIs (Tsao *et al.*, 2006).

Furthermore, some researchers recorded that sertraline appeared safer than tricyclic antidepressants in the overdoses (Klein-Schwartz and Anderson, 1996). Sertraline is a naphthylamine derivative that interacts with presynaptic sites on serotonergic neuronal membranes to potently and selectively block the uptake of serotonin (5-HT) in vivo and in vitro (Koe *et al.*, 1983 & 1990). Various studies recorded that the sertraline is prescribed and involved in many spinal-mediated processes including locomotion and nociception (Barbeau and Rossignol, 1991; Willis and Westlund, 1997; Schmidt and Jordan, 2000). In addition, the serotonin may affect the spinal cord functions; depend on the dose used and detecting the response of treatment (Brumley *et al.*, 2007).

Food and Drug Administration organization (FDA) published results of a study on Dec, 27, 2014: (24, 591) about the side effects of sertraline on depressed patients and concluded that (2%) of people who are treated with sertraline are getting improvements in depression mode, but it was associated with spinal cord compressin.

Brumley *et al.* (2007) reported that the spinal mechanisms of sensation and behavioural changes in relation to serotonin concentration in the lumbrosacral region of the spinal cord of an adult rat after treatment with sertraline.

Ginger "*Zingiber officinale Rosc.*" belongs to a tropical and sub-tropical family-zingiberaceae, originates from South-East Asia and is introduced to many parts of the globe, has been cultivated for thousands of years as a spice and for medicinal purposes (Park and Pizzuto, 2002).

Ginger has a rhizome or root. It is typically consumed as a fresh paste, dried powder, slices preserved in syrup, candy or for flavouring tea. In many countries fresh ginger is used to prepare vegetables and as a flavouring agent for beverages and many other food preparations (Shukla and Singh, 2007). It has been used extensively for more than 2500 years in china for headache, nausea and common cold (Grant and Lutz, 2000) and in the Mediterranean (Sharma and Clark, 1998) and western countries in herbal medicine practice for the treatment of arthritis, rheumatologic conditions and muscular discomfort (Bordia *et al.*, 1997; Langer *et al.*, 1998). Moreover, Abdel-Aziz *et al.* (2006) reported that ginger can act on the serotonin (5- HT_3) receptor ion-channel complex.

The present work aimed to evaluate the possible protective role of ginger against the side effects of sertraline.

MATERIAL AND METHODS:

Animals:

Normal forty male albinos Wister mice aged between 6 and 8 weeks, weighing approximately ± 25 gm each were obtained from the Faculty of Science, King Saud University, Kingdom of Saudi Arabia. These animals were caged as 5 mice per cage at 21 ± 3C^o and a relative humidity of 50 ± 15% with a 12-h light: 12- h dark cycle, received a standard pellet laboratory rodent diet and tap water *ad libitum*, housed in the biology department, college of Science, University of Dammam, and acclimatized for one week before starting the experiment. Handling of animals is complied with the ethical guidelines of the University of Dammam ethical committee.

Experimental design:

Animals were divided into 4 groups (5 mice/each). Group 1 (G1) is a normal control group including mice that received a daily oral ingestion of saline solution (2 ml) for 28 days (time of the experiment). Group 2 (G2) includes mice that received alcoholic extract of ginger orally (10% of 50 mg/L). Group 3 (G3) includes mice that received sertraline (0.13 mg/kg/BW) orally. Group 4 (G4) includes mice ingested sertraline (0.13 mg/kg/BW), the dose was calculated according to Paget and Barnes (1964) and after 1 hour ginger extract (10% of 50 mg/L) was orally given according to Fuhrman *et al.* (2000). Duration of experiment was 28 consecutive day. After 24 h from the last ingestion, the mice were sacrificed and dissected. The spinal cord was taken and processed for the histopathological and immunohistochemical studies by the light microscope. Also, the spinal cord tissue was processed for ultrastructural examination by transmission electron microscope. The light and electron microscopic preparations were carried out at the research unites of the Faculty of Science, Dammam University and King Faisal University, KSA.

Chemicals and doses:

All chemicals were purchased from Sigma, Aldrich, St. Louis, USA:

(I) Sertraline (Zoloft®). Therapeutic dose of sertraline is 75 mg for human (Mula, 2013). It was purchased from Sigma- Aldrich, St. Louis, Mo, USA.

(II) Mouse monoclonal antibodies of neurofilament NF (2 F11) were manufactured by Roche. Diagnostics Limited, Charles Avenue. Burgess Hill.

(III) Ginger powder was purchased from Sigma- Aldrich, St. Louis, Mo, USA. The experimental dose (10% /50 mg/L).

Light microscopic study:

a) Haematoxylin and Eosin (Bancroft and Stevens, 1996).

Parts of the cervical region of the spinal cord were excised, fixed in 10% formal saline, processed and embedded in paraffin sections, and cut at 5 µ thickness. Paraffin sections were subjected to the following stains:

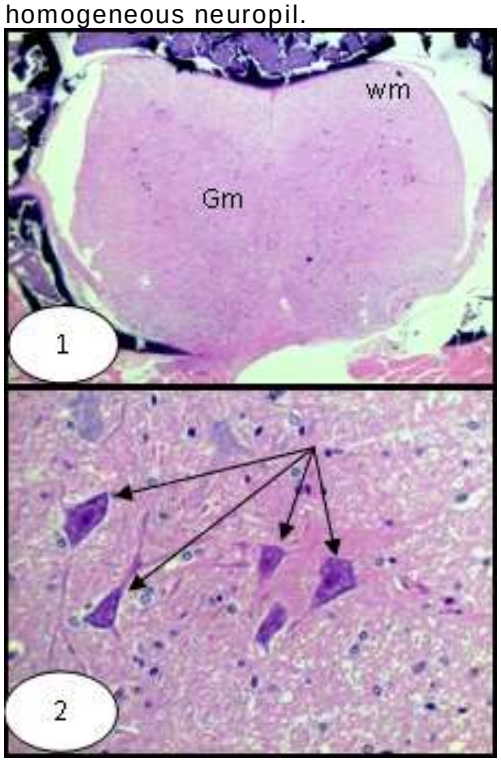
b) Immunohistochemical methods (Prophet *et al.*, 1992; Bancroft and Gamble, 2008). Paraffin sections were deparaffinised in xylene, dehydrated in descending grades of alcohol and immersed in 0.3% hydrogen peroxide methanol to block endogenous peroxidase activity. Sections were then washed in phosphate buffered saline, incubated for 3-5 minutes in citrate buffer in the microwave at 100ºC followed by washing in phosphate buffer and incubated for 1 hour in monoclonal mouse antibody NF clone (2F11). The sections were rinsed in biotinylated secondary antibody for 15 minutes followed by washing with phosphate buffer and Avidin-biotin for 15 minutes. Sections were rinsed in (red brown colour) DAB CM (3-3 diaminobenzidine) for 3 minutes, then washed in running water. These sections were countered stained with Mayer's HX, dehydrated in ascending grades of alcohol, cleared in xylene and mounted in Canada balsam. The sections were then examined under light microscope.

C) Ultrastructure preparations: fine pieces from the spinal cord tissues were immersed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer (PH 7.3) for 4 hours, then fixed in 1% osmium tetraoxide in 0.1 M cacodylate buffer (PH 7.3) for 2 hours stained with lead citrate and uranyl acetate (Robertson *et al.*, 1978).

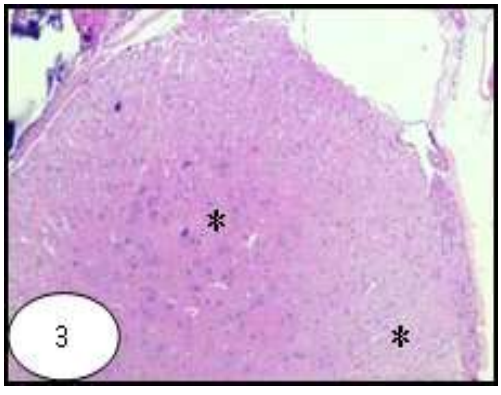
RESULTS:

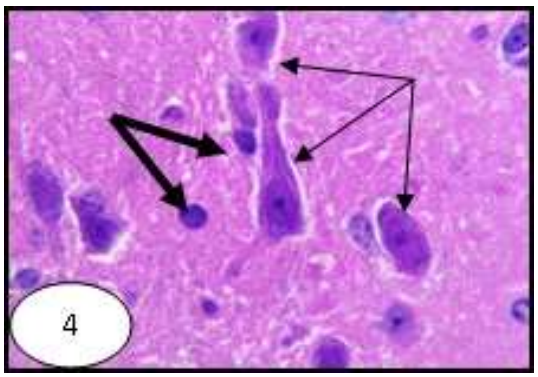
Histopathological results:

The light microscopic examination of sections of the spinal cord (cervical region) stained with Haematoxylin and Eosin revealed the variation among the four groups of the study. The control group G1 illustrates normal histological structure of the spinal cord. The white matter contained myelinated nerve fibres with central axons (Fig. 1).The gray matter appeared well organized and various forms of multipolar neurons were observed at the dorsal and ventral horns of the gray matter (Figs 1 & 2). The examination of tissue sections of animals treated with ginger extract (G3) showed more or less normal control architecture (Figs 3 & 4). Homogeneous and organized gray and white matters were clearly noticed (Fig. 3). Also the multipolar normal neurons could be observed with their large central nuclei (Fig. 4) and they were associated with various small glial cells. On the other hand, examination of the spinal cord sections taken from animals treated with sertraline (G3) revealed a high degree of markedly observed neuropil degeneration (Figs 5 & 7). Rupture of some blood capillaries and damage of most of the axons of the myelinated nerve fibres were also noticed (Fig. 7). Furthermore, the nerve cells displayed various cellular changes such as vacuolization of the neuron's cytoplasm (Fig. 6). Also some neurons appeared necrotic with shrunken irregular nucleus. Degeneration of the nuclear chromatin of the glial cells was markedly observed (Fig. 6). In the group of mice treated with sertraline then followed by ginger (G4), a high degree of the histological architecture were improved, especially in the white matter that were rich in normal axons of myelinated nerve fibres and glial cells (Figs 8 & 9). In addition, the grey matter comprised well developed normal multipolar neurons, glial cells with normally oriented chromatin, and homogeneous neuropil.

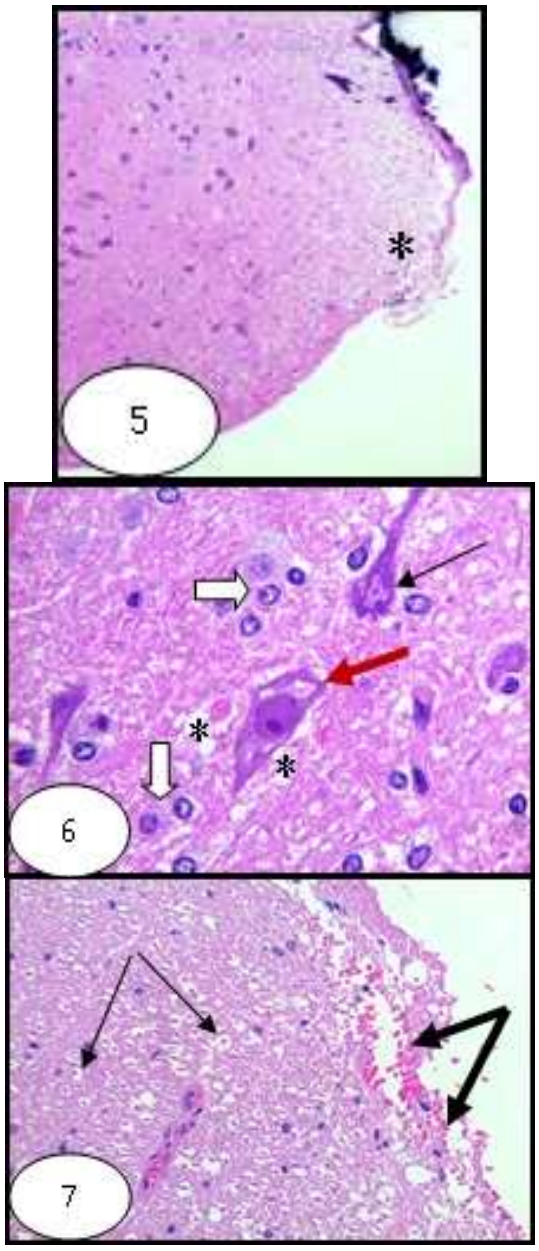


Figs 1 & 2. Light micrographs of the spinal cord (cervical region) of mice of G1 control group revealing gray matter (Gm) and white matter (wm), as well as, various types of multipolar neurons (arrows), H & E; 1 X 10, 2 X 40.

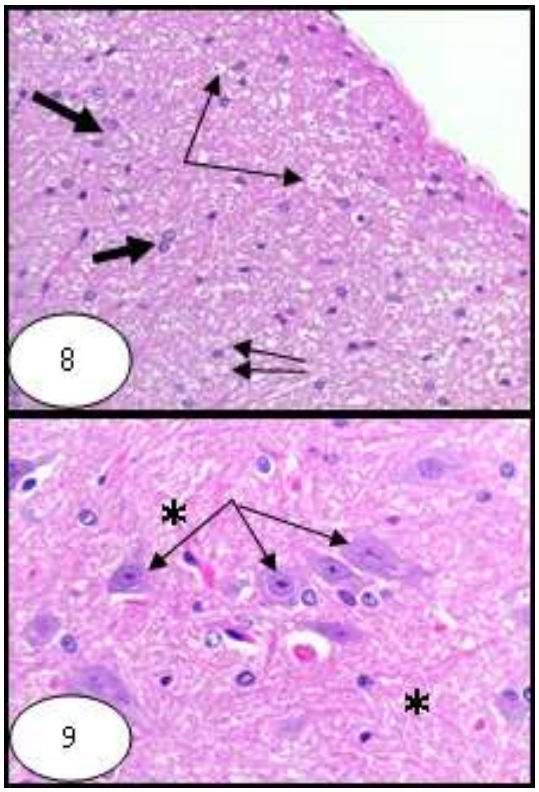




Figs 3 & 4. Light micrographs of the spinal cord (cervical region) of mice of G2 ginger treated group showing more or less normal architecture of the neuropil (*), nerve cells (arrows) and associated small glial cells (thick arrows), H & E; 3 X 40; 4 X 100.



Figs 5, 6 &7. Light micrographs of the spinal cord (cervical region) of mice of G3 sertraline treated group showing high degree of degeneration (*) {Fig.5}, necrosis of some neurons (arrows), vacuolation of the neural cytoplasm of other neurons (red arrow), non-homogeneous and vacuolated neuropil and glial cells with nuclear degenerated chromatin (white arrows) were noticed (*) {Fig.6}, hemorrhage of the blood vessels (thick arrows) and damage most of the axons in the white matter (thin arrows) {Fig.7}. (H&E; X 5= 10, X 6= 100, X 7= 40)



Figs 8 & 9. Light micrographs of the spinal cord (cervical region) of mice of G4 sertraline followed by ginger treated group showing improvement of the histological architecture of the white matter which appeared with well-developed axons (thin arrows) and normal glial cells (thick arrows){Fig.8}. Disappearance of the nuclear chromatin degeneration of glial cells and well developed normal multipolar neurons (arrows) and homogeneous neuropil (*) were observed {Fig.9}. (H & E; X 8= 40, X 9= 100)

Immunohistochemical results:

Monoclonal mouse antibodies (NF 2F11) were used to investigate the neurofilament protein immunohistochemically. The neurofilament protein is the main constituent of the neurofilaments that are present in the cytoplasm of the nerve cells and in the nerve fibres of the gray matter's neuropil. The cytoplasm of the multipolar neurons of control normal group (G1) (Fig. 10) and ginger treated group (G2) (Fig. 11) showed highly intense reaction. On the contrary, the sections of sertraline treated group (G3) illustrated very weak reaction (Fig. 12). In the group of mice treated with sertraline, then followed by ginger (G4), intense reaction was seen which most likely is considered an evidence of improvement of the cellular neurofilament protein NF in the neurons and gray matter (Fig. 13).

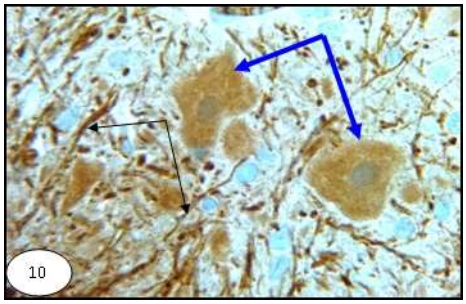


Fig. 10. Light micrographs of the spinal cord (cervical region) of mice of Monoclonal mouse antibodies of NF for demonstration of the neurofilament proteins in the normal control group (G1) showing normally positive intensive coloration in the cytoplasm of the neurons (thick arrows) and most of the nerve fibers (thin arrows) characterizing the gray matter of the spinal cord, X 100.

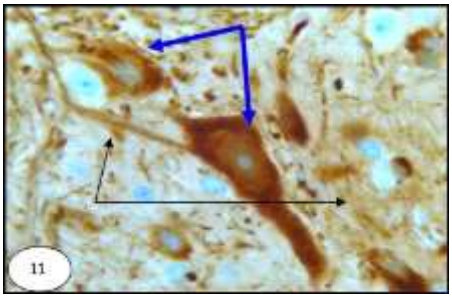


Fig. 11. Light micrographs of the spinal cord (cervical region) of mice of Monoclonal mouse antibodies of NF for demonstration of the neurofilament proteins in ginger treated group (G2) showing normal intense positive reaction in the cytoplasm of the neurons (thick arrows) and in most of the nerve fibres (thin arrow) characterizing the gray matter of the spinal cord, X 100.

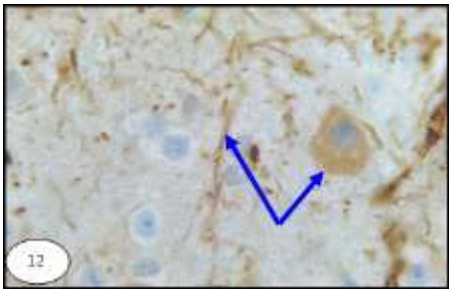


Fig. 12. Light micrographs of the spinal cord (cervical region) of mice of Monoclonal mouse antibodies of NF for demonstration of the neurofilament proteins in the sertraline treated group (G3) showing very weak reaction (arrows), X 100.

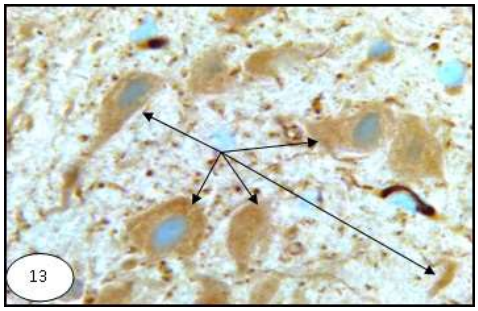


Fig. 13. Light micrographs of the spinal cord (cervical region) of mice of Monoclonal mouse antibodies of NF for demonstration of the neurofilament proteins in G4 sertraline treated group followed by ginger showing more or less normally stained neurons and nerve fibres (arrows) similar to the normal control sections, X 100.

Ultrastructural results:

The ultrastructural examination of the tissue sections revealed marked alterations in the cellular structure of the spinal cord after treatment with sertraline. In control sections the neurons appeared with central nucleus and prominent nucleolus (Fig. 14). The nucleus was surrounded by abundant cytoplasm rich in organelles such as Golgi apparatus and mitochondria (Fig. 15). The synaptic areas comprised prominent clefts, several clusters of the synaptic vesicles and well developed mitochondria (Fig. 16). Tissue sections treated with sertraline displayed shrunken and laterally located nucleus. The surrounding cytoplasm was remarkably observed with damaged cellular organelles (Fig. 17). Also the synaptic sites showed several structural changes such as malformed mitochondria, wide synaptic cleft and scarce synaptic vesicles (Fig. 18). Moreover damaged myelinated nerve fibres were also noticed (Fig. 19). Sertraline followed with ginger extraction treated sections showed a high degree of improvement (Fig. 20). More or less normal neurons were observed with central euchromatic nucleus and homogeneous cytoplasm rich in well developed cellular organelles (Fig. 20). The normal synaptic sites with vesicles, cleft and mitochondria were clearly noticed (Fig. 21). In addition well developed myelinated nerve fibres were markedly observed (Fig. 22).

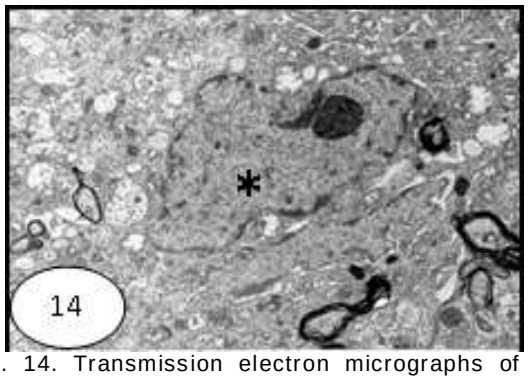


Fig. 14. Transmission electron micrographs of the spinal cord (cervical region) of mice of G1 control group and ginger treated animals groups showing one of the neuron in the gray matter (*) surrounded by homogeneous neuropil, X 8000.

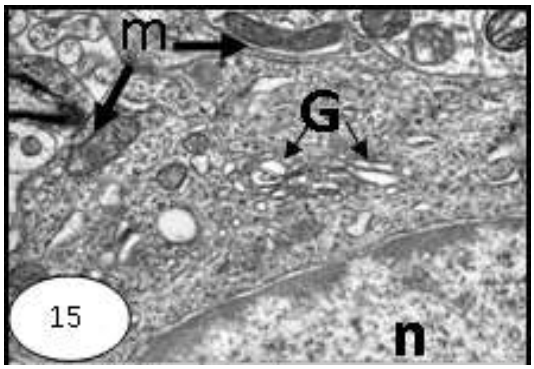


Fig. 15. Transmission electron micrographs of the spinal cord (cervical region) of mice of G2 ginger treated animals groups showing enlarged part of the cytoplasm with the cellular organelles such, as well developed mitochondria (m), Golgi (G) and nucleus (n), X 30000.

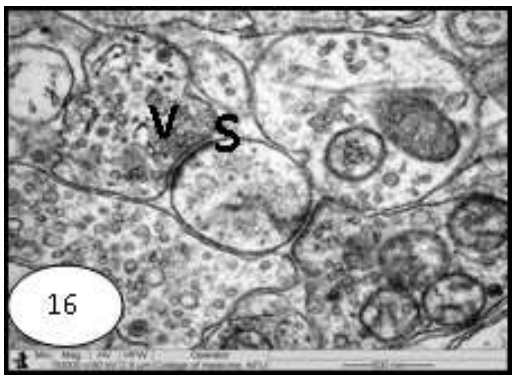


Fig. 16. Transmission electron micrographs of the spinal cord (cervical region) of mice of G1 control group showing synaptic sites (s) rich in synaptic vesicles (v) and well developed mitochondria (m), X 50000.

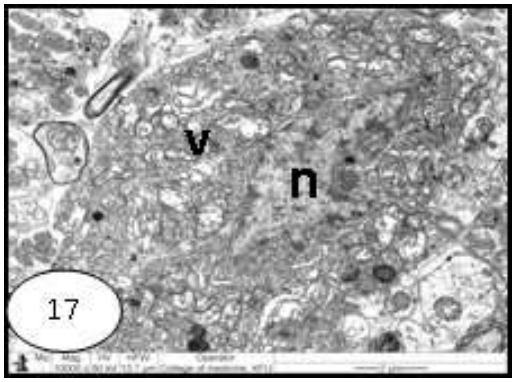


Fig. 17. Transmission electron micrographs of the spinal cord (cervical region) of mice of G3 sertraline treated group showing necrotic nerve cell with pyknotic shrunk nucleus (n) and vacuolated cytoplasm (v), (X= 10000)

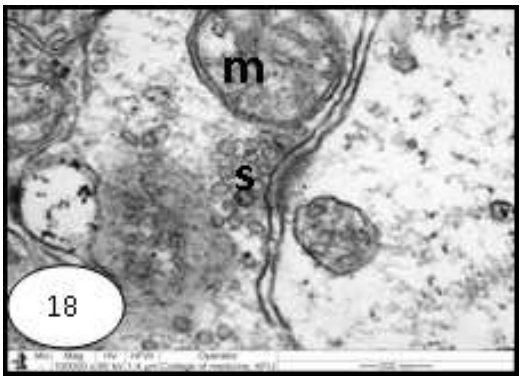


Fig. 18. Transmission electron micrographs of the spinal cord (cervical region) of mice of G3 sertraline treated group showing the synaptic site (s), slight damaged mitochondria (m), X 10000.

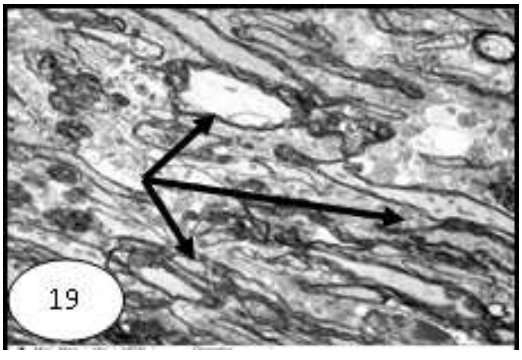


Fig. 19. Transmission electron micrographs of the spinal cord (cervical region) of mice of G3 sertraline treated group showing demeylination of the myelinated nerve fibres (arrows), X 4000.

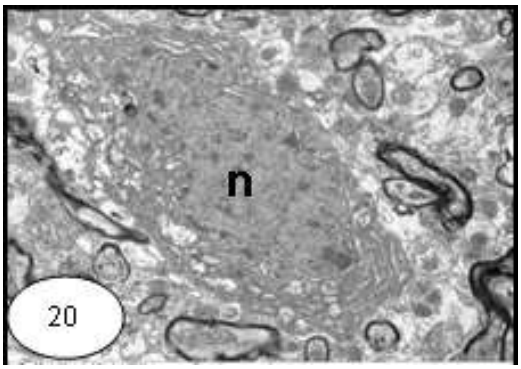


Fig. 20. Transmission electron micrographs of the spinal cord (cervical region) of mice of G4 sertraline treated group followed by ginger showing neuron (n) surrounded by homogeneous neuropil, X 8000.

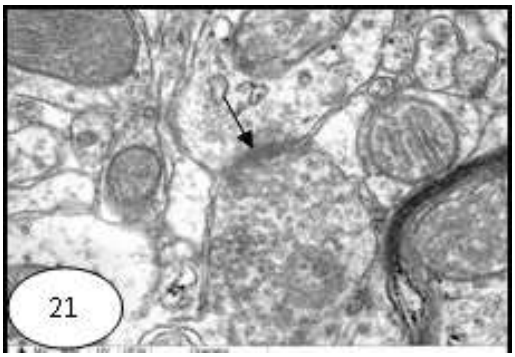


Fig. 21. Transmission electron micrographs of the spinal cord (cervical region) of mice of G4 sertraline treated group followed by ginger showing well developed synaptic sites (arrow) highly rich with vesicles, X 50000.

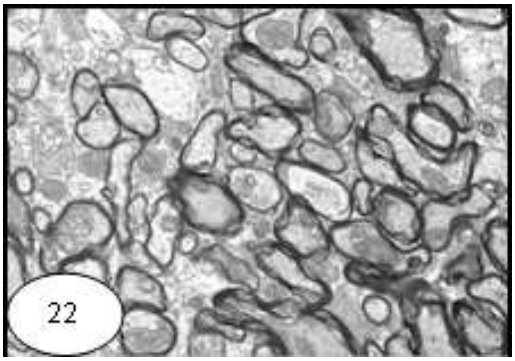


Fig. 22. Transmission electron micrographs of the spinal cord (cervical region) of mice of G4 sertraline treated group followed by ginger showing myelinated nerve fibres enwrapped with myelin sheath, X 10000.

DISCUSSION:

The present study was carried out on mice to investigate the side effects of the equivalent human therapeutic dose of sertraline as an antidepressant drug. Sertraline is one of the serotonin selective reuptake inhibitors (SSRIs). Furthermore, one of the important studies reported that SSRIs

could change personality and mood in the absence of disorder suggesting these may be critical psychological mechanisms in pharmacological interventions (Simmons and Allen, 2011). In addition , sertraline acts on the synaptic sites in the central nervous system tissues leads to remarkable change of serotonin (5-HT) level at the synaptic sites (Preskorn, 1996) and causes mood changes. Serotonin was discovered to facilitate locomotion (Feraboli-Lohnherr *et al.* 1999) and spinal plasticity (Crown and Grau, 2005). Various studies investigated the effects of serotonin concentrations in rat spinal cord to explain the spinal mechanisms of sensation and behavior (Brumley *et al.*, 2007; Růžička *et al.*, 2013). They concluded that serotonin causes change in spinal activity. Some studies (Beyer and Cremers, 2008) recorded that the acute and sub-chronic administration of sertraline results in different pharmacological effects such as decreasing of 5-HT levels in some parts of the brain, and decreasing of the serotonergic neurotransmission (El Mansari *et al.*, 2005). It is worth mentioning that, studies of Preskorn (1996) are in agreement with some of our ultrastructural study findings such as the damage of the synaptic sites, decrease of the synaptic vesicle and malformation of the mitochondria at the damaged synaptic sites in the spinal cord. Furthermore, several studies have evidence that SSRIs administration causes many neuronal changes in receptor function (Nic Dhonnchadha *et al.*, 2005; Yamauchi *et al.*, 2006). This evidence agrees with the present study results and confirmed by the histological alterations which appears as cellular changes of the spinal cord neurons. Several studies used sertraline for 28 days (Knutson *et al.*, 1998; Tse and Bond, 2001) and reported various mood changes as affiliativeness, self directedness and socialization. The applied time of our experiment was 28 days, and the results provided us with adequate information to investigate the side effects of sertraline. Moreover, gene study investigations reported that the 5-HTTLPR, a functional polymorphism of the 5- flanking region of the 5-HT transporter gene, has a role in vulnerability to depression (Caspi *et al.*, 2010; Karg *et al.*, 2011) and response to SSRIs treatment (Huezo-Diaz *et al.*, 2009; Keers *et al.*, 2011). Reports of other previous studies would confirm the nuclear changes observed at the necrotic cells and the nuclear chromatin degeneration of the glial cells in the gray matter of the spinal cord especially in the group G3 (Lee *et al.*, 2015).

Moreover, it was found that there is certain relation between the SSRIs as sertraline, and fluoxetine, and the immobility limitation and swimming behaviour enhancement (Page *et al.*, 1999). Thus, the forced swimming test is a behavioral test in rodents that indicates the efficiency of many types of antidepressant treatments (Detke *et al.*, 1995; Lucki, 1997). Therefore, it can be confirmed that the spinal cord is responsible for locomotion as a nervous function (Schmidt and Jordan, 2000). From the previous readings, it is concluded that endogenous 5-HT is affected with sertraline. The cytoplasm vacuolization of the spinal cord neurons at the gray matter and neuropil degeneration providing further evidence for the effectiveness of the sertraline treatment in induction of some cellular neural changes in the spinal cord of the mice.

Mammalian neurofilaments are present in neurons of the gray matter of the central nervous tissues such as the spinal cord, granule cells of the cerebellum (Vitadello and Denis-Donini, 1990). The neurofilaments can be visualized and demonstrated with anti-neurofilament antibodies (Shaw *et al.*, 1981; Trojanowski *et al.*, 1986). The present finding revealed apparent changes in the neurofilaments content demonstrated with anti- NF antibodies in the nerve cells and nerve fibres of the experimental treated animals with sertraline, and the consequent improvement after treatment with ginger extract. In similar studies, Abdel-Aziz *et al.* (2006) reported that the ameliorative effects of ginger are probably due to its action on serotonin receptors ion channel complex.

In one of the most important studies, Růžička *et al.* (2013) reported that the decrease in neurofilaments in injured spinal cords is most likely due to changes in serotonin level. On the other hand, treatment with combination of the human fetal neural stem cells and hydrogels modified with serotonin restores the damaged neurofilaments.

Improvement of the subcellular organelles at the ultrastructural level organelles, such as the appearance of normal nuclei, homogeneous neuropil and well developed synaptic sites with its characteristic synaptic vesicles and clefts, and the disappearance of the cytoplasm vacuolation, were markedly observed after treatment with ginger. Our results are confirmed with results of Abdel-Aziz *et al.* (2006) that established the presence of an indirect effect of ginger active constituents on the serotonin 5-HT3 receptors (serotonin receptor subtype). The effect of ginger constituents (6,8 and 10 gingerol as well as 6 shogaol) on the 5 – HT3 receptor ion – channel complex,are probably by biding to a modulator site other than that of the serotonin binding site (Huang *et al.*, 1991). In the present study, the use of different techniques such as histological, immunohistochemical and ultrastructural methods, may give a good insight on the correlation between the effect of the ginger on the serotonin receptors and

the effect of sertraline dependent alterations. Thus, the observed amelioration in the neurofilaments and the synaptic sites may be due to inhibition of 5 – HT3 receptor function by different mechanisms (Molderings *et al.*, 1996; Barann *et al.*, 1999).

CONCLUSION:

This study illustrated the ginger protective and ameliorative effects against cellular changes, such as; neurofilaments expression, synaptic sites and various cellular organelles alterations in the spinal cord tissue of adult mice, that always develope as side effects of the sertraline therapeutic doses.

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التأثير الواقى العصبى للزنجبيل ضد السيرترالين كأحد العقاقير المضادة للإكتئاب والذى يستحث أضرار فى الحبل الشوكى للفئران

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يعتبر السيرترالين من العقاقير المضادة للاكتئاب والتى تستخدم لعلاج الاكتئاب. ومع ذلك، هناك العديد من الآثار الجانبية خلال استخداماتها في العلاج. الزنجبيل هو عبارة عن مادة طبيعية لديها العديد من الأدوار الحيوية الفعالة مثل زيادة المناعية، وزيادة مضادات الأكسدة، وكسح الجذور الحرة ، وأيضا يعمل كمادة مضادة للالتهابات. ركزت هذه الدراسة على توضيح التغيرات النسيجية والتركيبية الدقيقة والكيمياء النسيجية المناعية في الحبل الشوكي في ذكور الفئران البيضاء بعد تناولهم لمادة السيرترالين لتوضيح الدور الوقائي لمستخلص الزنجبيل. تم تقسيم أربعين من ذكور الفئران البيضاء البالغة إلى أربع مجموعات: مجموعة (1) تناولت ماء مقطر، المجموعة (2) تناولت 50 ملجم / لتر (10٪) من مستخلص الزنجبيل ، مجموعة (3) تناولت عقار سيرترالين (0.13 ملجم / كجم / وزن الجسم) , مجموعة (4) تناولت عقارالسيرترالين وبعد ساعة تناولت مستخلص الزنجبيل. تم إعطاء هذه الجرعات المختلفة يومياً عن طريق الأنبوبة المعدية لمدة 28 متتالية. تم ذبح الحيوانات وأخذ عينات النخاع الشوكي (المنطقة العنقية) و معاملتها و تحضيرها للفحص النسيجي العام بالمجهر الضوئى والمجهر الإلكترونى النافذ. وقد أسفرت النتائج عن وجود العديد من التغيرات النسيجية والتركيبية الدقيقة فى المجموعات المعاملة بعقار السيرترالين فى الخلايا العصبية الحركية والحسية من الحبل الشوكي. كما لوحظ أيضا تغيرات فى بروتينات الخيوط العصبية فى الخلايا العصبية باستخدام طرق الكيمياء النسيجية المناعية. كما أظهرت النتائج بأن الزنجبيل يقلل من الأثار الضارة الناتجة عن استخدام عقار السيرترالين على المستوى النسيجي والتركيبي الدقيق والمناعي .