Costus improves atorvastatin-induced myotoxicity in rats: Histopathological, Ultrastructural, and biochemical studies

Original Article

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ABSTRACT

Background: Hyperlipidemia is the main cause of cardiac arrest and death; atorvastatin is the best medicine for its treatment. Increase its use has led to the appearance of side effects especially muscles. Costus is a medicinal herb that prevents the risks of poisoning that occur because of the use of atorvastatin. The aim of this study is to evaluate the costus extract against the myotoxicity of atorvastatin on male albino rats.

Methods: Eighty adult albino rats were used, divided into four groups each is twenty rats, the first group as a control, given only water throughout the experiment. The second group was given Costus root extract at a dose (0.4 mg/kg) daily. The third group was given 50 mg/kg/day of atorvastatin liquified in pure water and the fourth group was given the extract of the root of the costus at a dose (0.4 mg/kg) daily with 50 mg/kg / A Day of atorvastatin liquefied in pure water daily 90 days, via a gastric tube. After the end of the experiment, rats were anesthetized and excision of extensor digitorum longus then evaluating histopathology of muscles by light and electron microscopes and evaluating serum cardiac enzymes, potassium, creatinine and serum (CPK).

Results: Significant abnormalities in all biomarkers of muscle toxicity with its degenerative changes and use of the root extract of costus with the sub-chronic intake of atorvastatin ameliorating signs of muscle toxicity.

Conclusions: Sub-chronic use of atorvastatin could cause myotoxicity On the contrary antioxidant costus may help to prevent atorvastatin-induced myotoxicity.

Key Words: Atorvastatin, biochemical histopathology, costus root extract, myotoxicity, ultrastructure.

Revised: 04 February 2024, **Accepted:** 31 May 2024

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ISSN: 1110-0559, December 2023, Vol. 7, No. 2.

INTRODUCTION

Increased blood cholesterol is one of the main causes of atherosclerosis, which may cause disease of coronary blood vessels, major central nervous system diseases and diseases among the peripheral vessels of the body, which encouraged scientists to find an effective treatment to treat excess cholesterol levels in the blood[1].

Atorvastatin is considered one of the statin drugs used in the reduction of cholesterol levels in the blood. The action of statins is the reduction of 3-hydroxymethylglutaryl-coenzyme which will limit the synthesis of cholesterol. In addition to that, it also surges the beneficial cholesterol level (HDL) which protects heart vascular disease[2]. Moreover, other effects include antioxidant and anti-inflammatory effects, decrease in coagulation response and immunomodulatory effect[3].

Also, endothelial protection by modifying cell membrane permanency and the mitochondrial role and decrease cholesterol level in the cellular membrane[4]. But to use atorvastatin safely is still under research and its beneficial use is still restricted because of its toxicity on muscle fibers that began from pain in muscular tissues to cellular damage in patient use of atorvastatin[5].

The most statins drugs are atorvastatin, pravastatin, rosuvastatin and Fluvastatin. Side effects of statin therapy, which can be more serious, include type 2 diabetes mellitus, nervous tissue pathological changes, severe cognitive effects, liver and kidneys cellular toxicity[6].

 DOI: 10.21608/jmh.2024.267722.1126

There is innovative complex treatment with a statin to reduce its potential side effects such as myotoxicity[7]. Recently, the intake of herbal medicines to protect against or treat diseases is related to old age. There is major progress in pharmacological findings over the ages leading to the presence of several produced medications. This reaffirms the value of medicinal ethnic plants to discover the drugs[8].

Medicinal plants are one of the medicinal sources from which new medicines are extracted to treat some different diseases, among which costus is a plant that contains several pharmacological properties like antioxidants, carcinogenic protective factors, anti-inflammatory, antidiabetics, dyslipidemia protective factors, liver protection, steroid and effects anti-microbial[9].

Indian medicinal plant as Costus specious used usually in the treatment of different diseases which are related to family Coastaceae (Zingiberaceae)[10] .There are two important types of costus which are white and black, the white is sweet and the Indian black is hotter, but the Indian type is bitter than the marine. The skins of the root are the active therapeutic product[11]. Roots of Costus speciosus have many properties as hepatoprotective action[9] and in the treatment of cough and asthma. In Saudi Arabia, the Costus species are known as astringent, bitter, expectorant, purgative, acrid, tonic, stimulant, anthelmintic, depurative and expectorant. Its rhizomes liquid is used in soothing on the forehead and treatment of pain. Its paste of roots is used for the treatment of boils and has sexual hormones and contraceptives[12].

Roots of Costus speciosus contained antioxidant chemical structures as Vitamin E, β- carotene, vitamin C and little amounts of calcium, potassium, magnesium and sodium[9]. .Also its leaves. Increase insulin action and decrease blood glucose so it's used in diabetes mellitus[13]. Statin has a greater effect in decreasing dyslipidemia in people who live in Asia also it has incidence acts when compared with other statins[14].

So, the present work aimed to evaluate the role of costus root extract on atorvastatin prolonged use-initiated toxicity of muscles of rats by evaluating grades of lactic acid dehydrogenase, creatinine phosphokinase, myoglobin, troponin I, potassium, creatinine, standers of oxidative stress and an assessment for histopathological and lesions of ultrastructures of extensor digitorum longus muscles.

MATERIALS AND METHODS

Eighty mature rats of albino type, both sexes, weigh between 250 - 350 g obtained by King Abdel Aziz University's animal home in Jeddah. During the experiment, the rats were fed water and regular rat pellets and were exposed to 12-hour day and night cycles. The rats were divided into four groups of twenty rats each. Group I is the control group that received water. Group II treated costus roots extract at a daily dose of (0.4 mg/ kg), group III treated atorvastatin dissolved in distilled water 50 mg/kg/day (equal 1 percent of LD50) and group IV received costus roots extract at a daily dose of (0.4 mg/ kg), daily with 50 mg/kg/ day of atorvastatin dissolve in distilled water daily for 90 days by gastric gavage. Costus root extract was acquired from a local market in Taif, Saudi Arabia and atorvastatin was available in 40 mg tablet form from Egyptian International Pharmaceutical Industries Co. (EIPICO, 10th of Ramadan City, Egypt)[15]. 100 g of roots were ground and 10 g of powdered Costus roots were added to 100 ml of hot water, which was then simmered for 3 - 5 minutes before being covered and put in a refrigerator at a temperature under 25^{o}C, this extract was applied to rats by gastric tube[16].

Blood sample collection:

The rats were anesthetized with diethyl ether once the experiment was completed and samples of blood were drawn from the eye using cover test tubes(Retro-orbital blood sample taken from orbital plexus). Then, the blood could coagulate at a temperature of the room 24°C for 20 - 25 minutes. Then samples were placed for 10 minutes in a centrifuge at 2500 rpm at 3 °C to separate the serum to throw clotting, then the serum was kept at -25 °C till examination.

By using analyzers to measure Troponin I and creatinine phosphokinase by using two mouse monoclonal antibodies in a sandwich format and were based on electrochemiluminescence immunoassay technology (ECLIA). It was a two-step procedure.

According to the manufacturer's instructions, they were performed using Elecsys 1010 and 2010 immunoassay analyzers. Measurement of myoglobin by immunoassays of enzymes[17].

Measurement of the level of serum creatinine by using commercial kits and measured on a clinical biochemistry autoanalyzer using

standard colorimetric procedures[18]. Lactic acid dehydrogenase levels in the blood are measured[19] and the Determination of serum potassium levels was done using diagnostic kits and routine spectrophotometric analysis[20].

Histopathological studies after the end of experiment excision of extensor digitorum longus of rats of the 4 groups after anesthetized fixation, cutting sections, washing, dehydrate in increasing degrees of alcohol, clarified in xylene, fixed in wax paraffin, a section at 3 - 6 m thickness and stain with Hematoxylin and Eosin and Mallory. A blinded pathologist inspected and assessed the muscular histological slides under a light microscope[21].

Ultrastructure studies Muscle tissue specimens were bathed and treated in glutaraldehyde at phosphate buffer at 3°C using a transmission electron microscope. The samples were then rinsed in 0.15 M phosphate buffer (pH 7.2) and fixed for 1 hour at 4°C in a 2 percent osmic acid solution in 0.15 M phosphate buffer. Acetone was used to dehydrate the specimens, which was followed by the inclusion of sodium.

RESULTS

Biochemical findings:

chloride. Soaked in epoxy, cutting blocks at 70 nm thickness with an ultramicrotome type LKB. For electron microscopy investigation, the slices were differentiated with uranyl acetate and lead citrate solutions[22].

Tissue preparation:

Homogeneity of muscle tissue in 4 ml of phosphate buffer at pH 7.4 and expelled for 15 minutes at 4°C at 10,000 g. Oxidative stress markers malondialdehyde, catalase, superoxide dismutase, glutathione peroxidase and glutathione were assayed in the supernatant[23].

Analysis of statistics:

version 17 of SPSS was used to perform the analysis of statistics. The findings were presented like means SD, analysis was done using one-way ANOVA and postage hoc many compared many tests to see if there was a difference in levels of biomarkers between groups, with a statistically significant *P* value of 0.05.

Considerations of ethics:

By selecting any suitable animal, high-quality care and animal welfare were always prioritized. For the experiment, a suitable sample size of animals was estimated to produce statistically valid results with the fewest number of animals. Painful operations were carried out under anesthesia. that the animals might be subjected to. Our animal care and administration standards meet or exceed the norms and standards set forth by international laws and regulations.

Table 1: Compares the effects of atorvastatin alone versus atorvastatin plus costus root extract on the mean and SD of several biomarker levels of toxicity in rat muscles:

	Group I (mean ± SD)	Group II (mean ± SD)	Group III (mean ± SD)	Group IV (mean ± SD)
Troponin-1 (ng/mL)	0.0031 ± 0.002	0.0039 ± 0.002	0.8110 ± 0.024*	0.1612 ± .012†
CPK (U/L)	280.2 ± 31.345	251.21 ± 8.301	701.8 ± 64.567*	301.74 ± 8.32†
Myoglobin (ng/ml)	130.2 ± 4.241	127.41 ± 2.101	302.1 ± 8.234*	138.1 ± 7.135†
Creatinine (mg/dl)	0.80 ± 1.012	0.79 ± 0.024	0.98 ± 0.276*	0.71 ± 0.123†
LDH (U/L)	156.46 ± 67.456†	129.12 ± 54.012	912.2 ± 67.123*	202.3 ± 11.012†
Potassium (meq/L)	5.01 ± 0.123	4.9 ± 0.234	2.3 ± 0.200*	4.8 ± 0.456†

CPK, creatinine phosphokinase; LDH, lactic acid dehydrogenase.

Table 1 shows a statistically significant rise in Troponin-1, Myoglobin, Creatinine and LDH in the third group when compared to the first and second groups, but a significant decrease in Troponin-1, Myoglobin, Creatinine and LDH in the fourth group when compared to the third group.

Table 2: Compares the effects of atorvastatin alone versus atorvastatin plus costus root extract on the mean and SD of several oxidative stress marker levels of toxicity in rat muscles:

	Group I (mean ± SD)	Group II (mean ± SD)	Group III (mean ± SD)	group IV (mean ± SD)
Catalase	40.21 ± 2.34	42.21 ± 2.03	18.09 ± 1.32*	38.05 ± 1.95†
Peroxidase	13.12 ± 2.02	14.18 ± 1.25	8.98 ± 0.78*	12.89 ± 2.02†
GSH glutathione	98.31 ± 2.02	99.04 ± 2.05	62.32 ± 2.99*	94.96 ± 1.99†
MDA: malondialdehyde	30.63 ± 0.44	31.11 ± 0.12	60.1 ± 21.09*	29.98 ± 2.54†
Superoxide dismutase	28.02 ± 2.01	29.24 ± 1.06	18.96 ± 0.31*	29.01 ± 2.01†

Table 2 showed that values catalase, peroxidase, glutathione and superoxide dismutase in group III (atorvastatin group) significantly decreased when compared to the groups I and II, whereas all these results significantly rise in group IV (atorvastatin with costus root extract) in comparison with group III (atorvastatin group). In contrast, the result of malondialdehyde (MDA) is significantly higher in group III when compared to groups I and II, which decreased in the fourth group (atorvastatin plus costus root extract) in comparison with group III.

Histopathological findings of (EDL):

The longitudinal section of (EDL) of rats groups I and II revealed normal structure (Figures 1 and 2), as well as the presence of normal collagen fiber (Figures 5 and 6). Group III of rats, received atorvastatin only, showed splitting myofibers in the extensor digitorum longus muscle. with sarcoplasm fragmentation, infiltration of cells, dense and necrotic central nuclei with remnants nuclei (Figure 3), as well as abundant collagen fibers surrounding the afflicted myofibers (Figure 7). In group IV, rats treated with costus root extract after atorvastatin, the longitudinal section of extensor digitorum longus (EDL) muscle exhibited recovery in damage and normal appearance. of muscle fibers like the control. (Figure 4) and rare collagen fibers of endomysium (Figure 8).

Examination of the transmission electron microscope of extensor digitorum longus:

In initial groups I and II of rats, the ultrastructure of the extensor digitorum longus muscle (EDL) revealed normal arranging of muscle fibrils with dark and light bands. Between two sequential z lines with oval nuclei and normal mitochondria, sarcomeres can be observed. (See Figures 9 and 10).

(EDL) of rats of group III, which treated atorvastatin only, showed deterioration, including nucleus atrophy, myofibril disorganization and degeneration and significant aggregation and swelling of mitochondria. mitochondrial cristae disappearance and electron-dense granules mitochondria, vacuolated mitochondria in the intermyofibrillar space and pyknotic nucleus in the intermyofibrillar space and disruption and loss of Z line (Figure 11).

The ultrastructure of the (EDL) muscle in group IV of rats, that received atorvastatin in combination with costus root extract was like that of the groups I and II. Sarcomeres, nuclei and mitochondria were all in good structure (Figure 12).

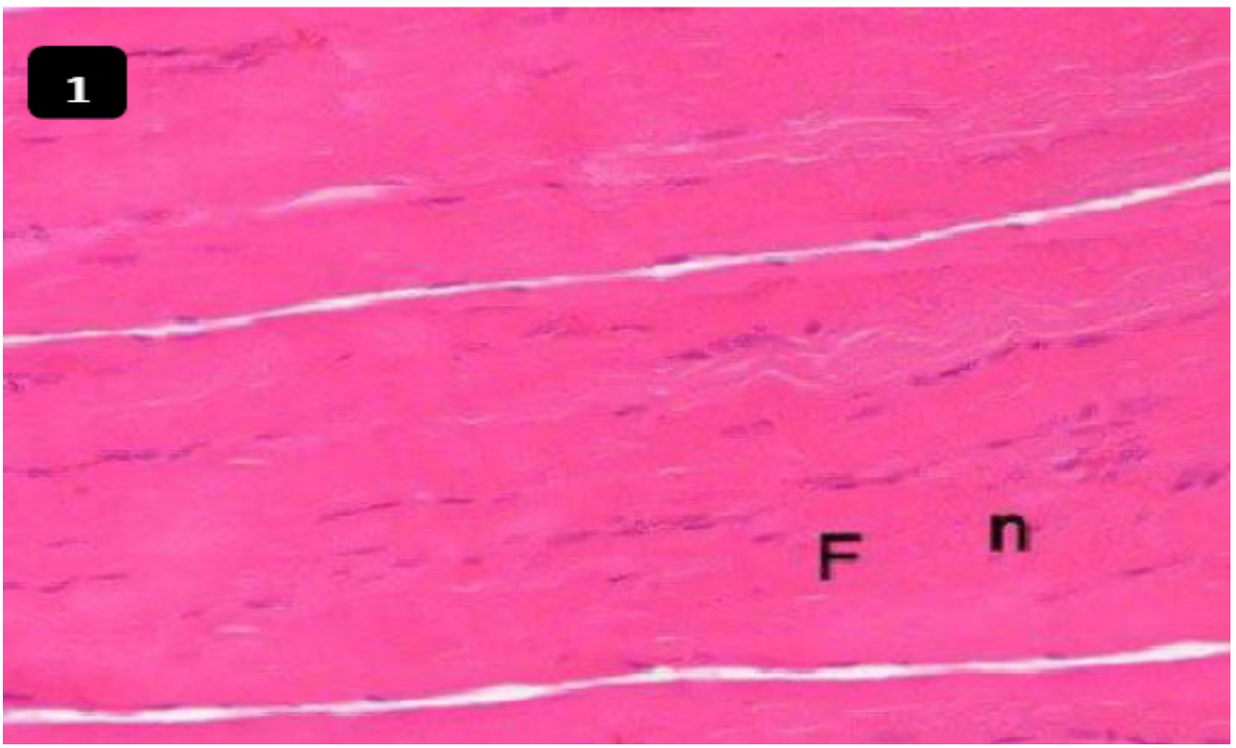

Figure 1: Light micrographs (LM) of a longitudinal section in group I of EDL muscle of rat revealing typical non-branching myofibers (F) and several long peripheral vesicular nuclei (n). Hematoxylin and Eosin ×400.

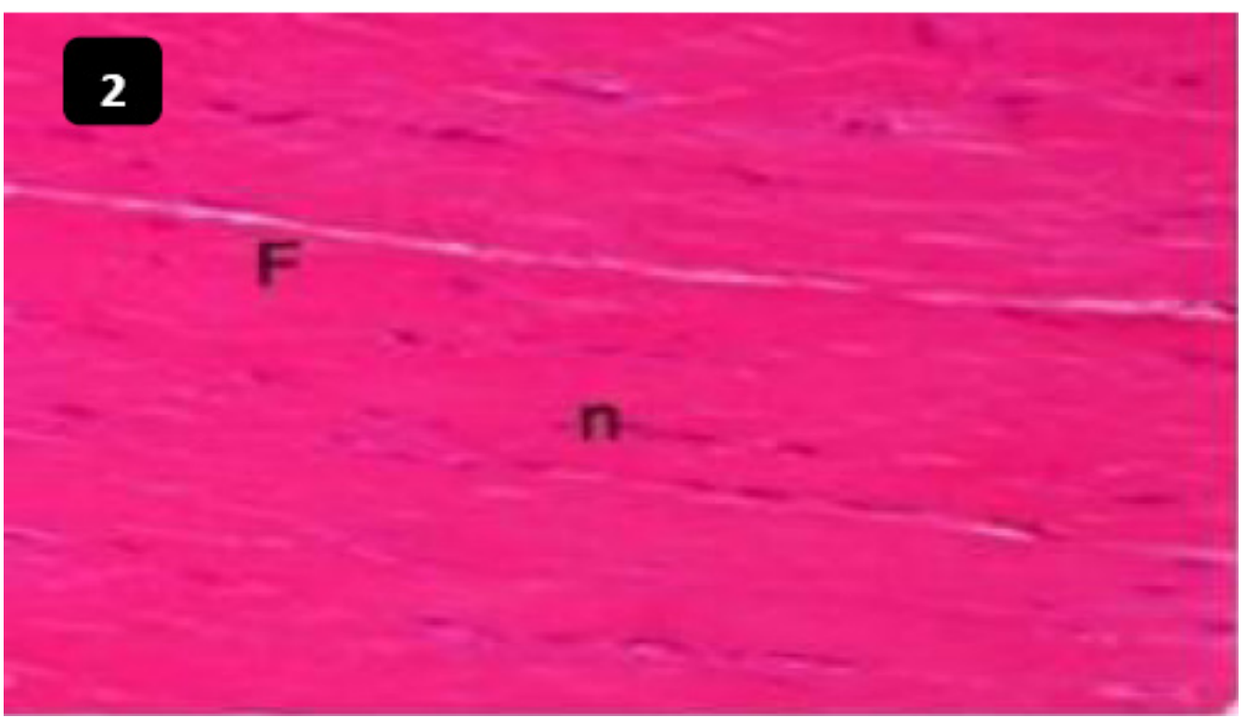

Figure 2: Light micrographs (LM) of a longitudinal section in group II of EDL muscle of rat revealing typical fibers of muscle (F) and several long peripheral nuclei (n). Hematoxylin and Eosin ×400.

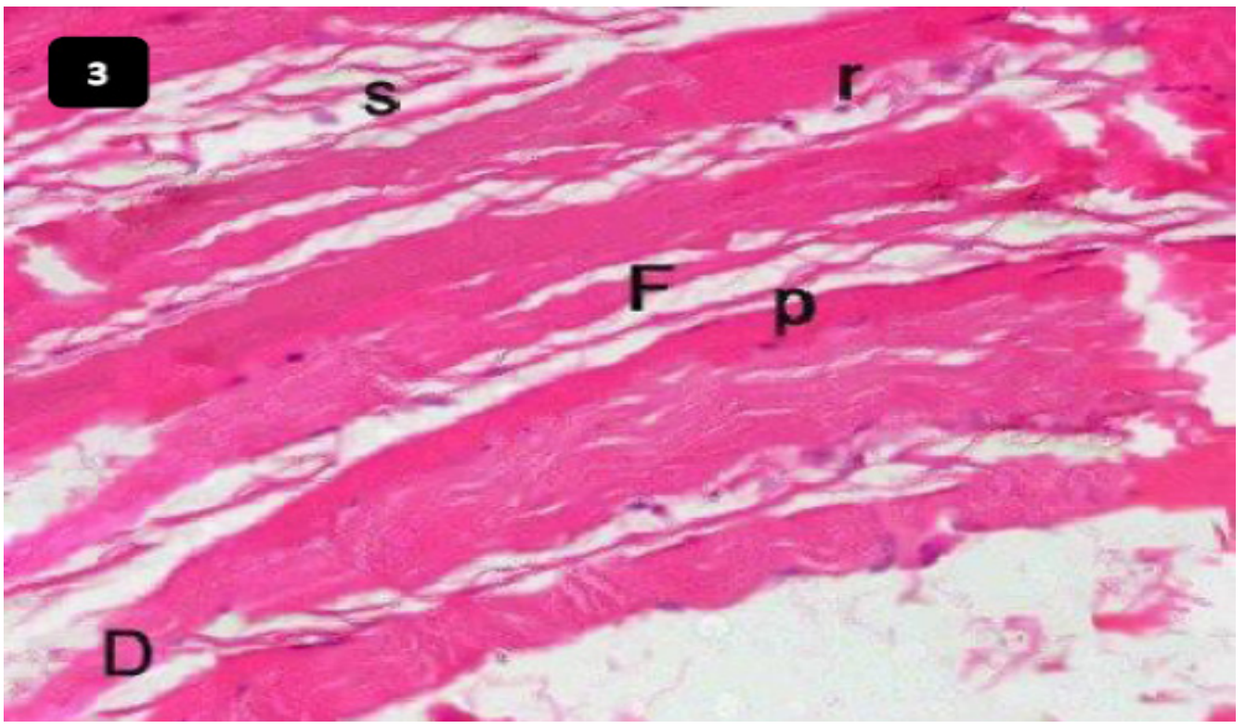

Figure 3: Light micrographs (LM) of a longitudinal section in group III of EDL muscle of rat revealing few myofibers (F), injured muscle fibers (D) with degenerating of myofibers (s), pyknotic nuclei (p) and the residues of degenerated nuclei (r). Hematoxylin and Eosin ×400.

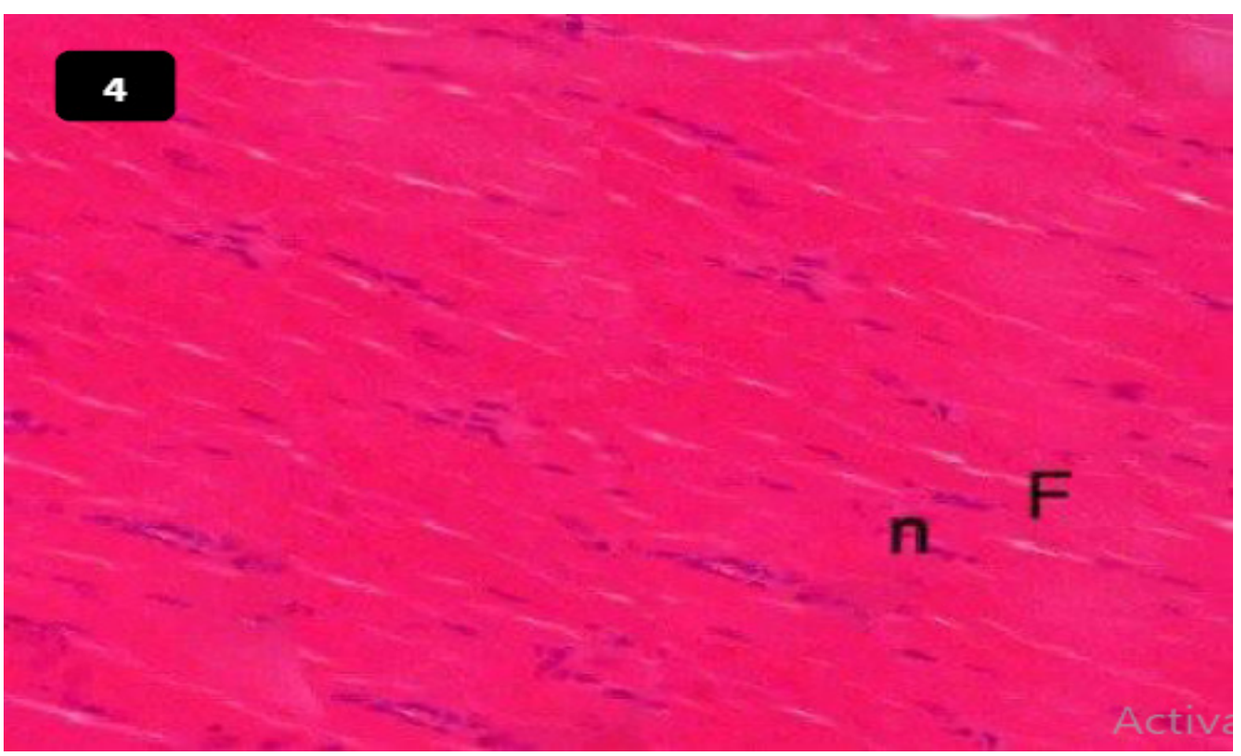

Figure 4: Light micrographs (LM) of a longitudinal section in group IV of EDL muscle of rat revealing nearly the typical view of whole myofibers (F) and several nuclei (n). Hematoxylin and Eosin ×400.

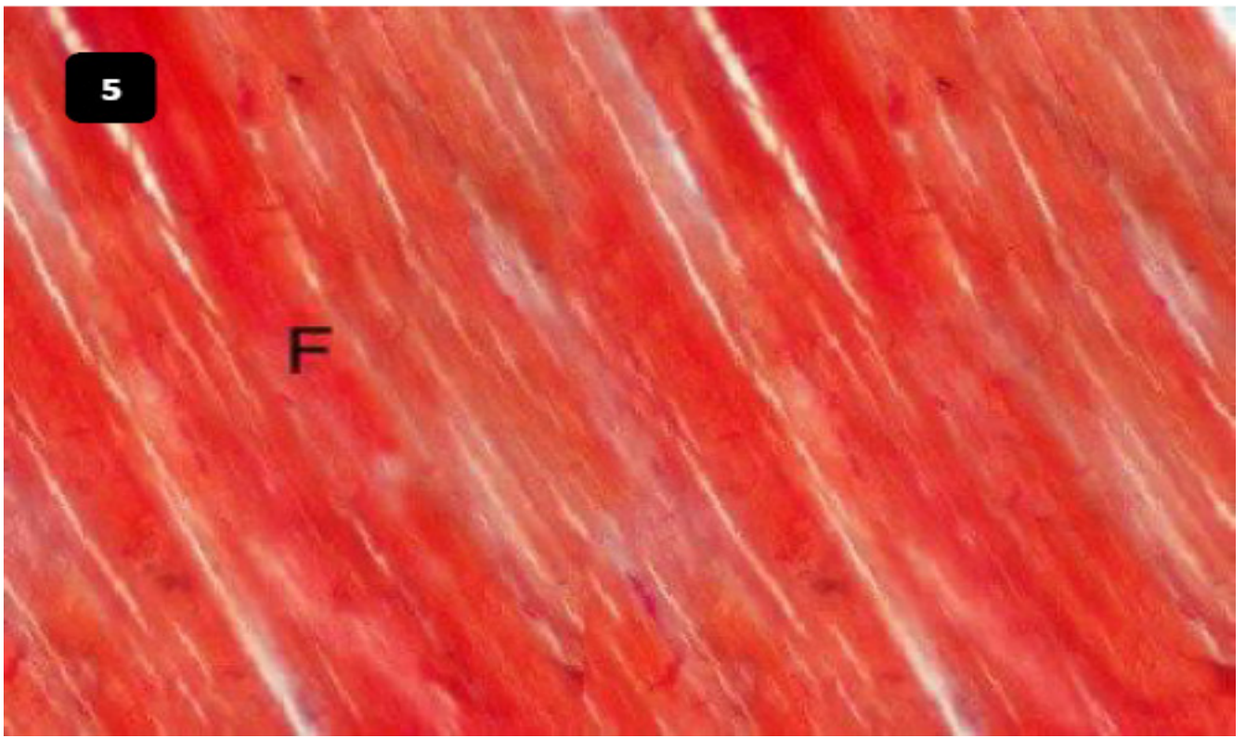

Figure 5: Light micrographs (LM) of a longitudinal section of group I of EDL muscle of rat revealing the normal arrangement of collagen fibers around non-branching myofibers (F). Masson trichrome ×400.

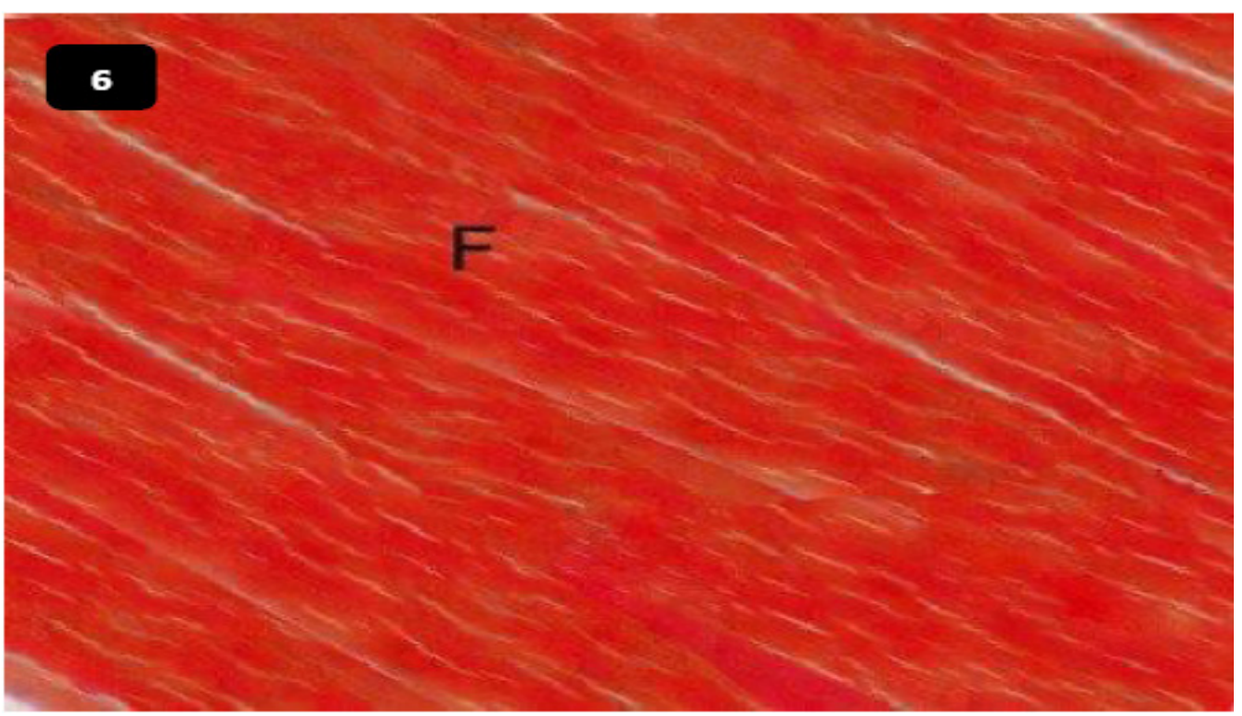

Figure 6: Light micrographs (LM) of a longitudinal section of group II of EDL muscle of rat revealing typical spreading of collagen fibers surrounding non-branching myofibers (F). Masson trichrome ×400.

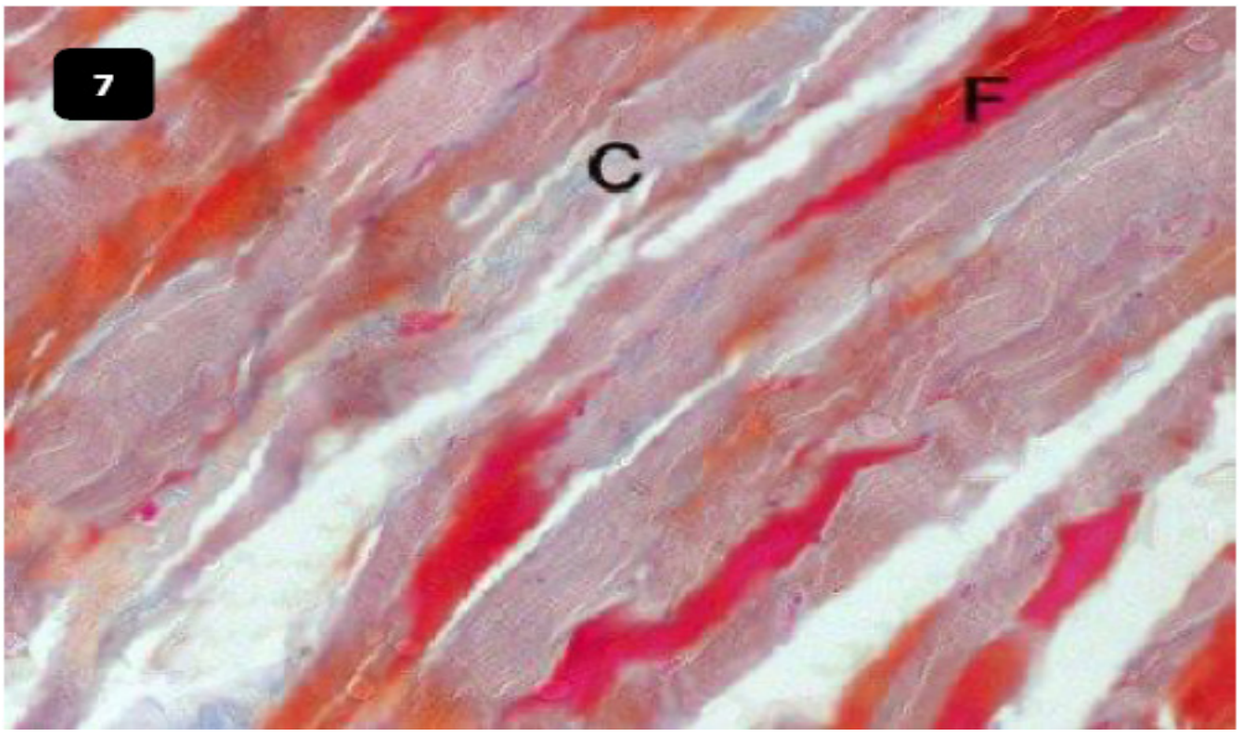

Figure 7: Light micrographs (LM) of a longitudinal section of group III of EDL muscle of rat revealing extreme blue collagen fibers(C) surrounding degenerated myofibers. (F) Masson trichrome ×400.

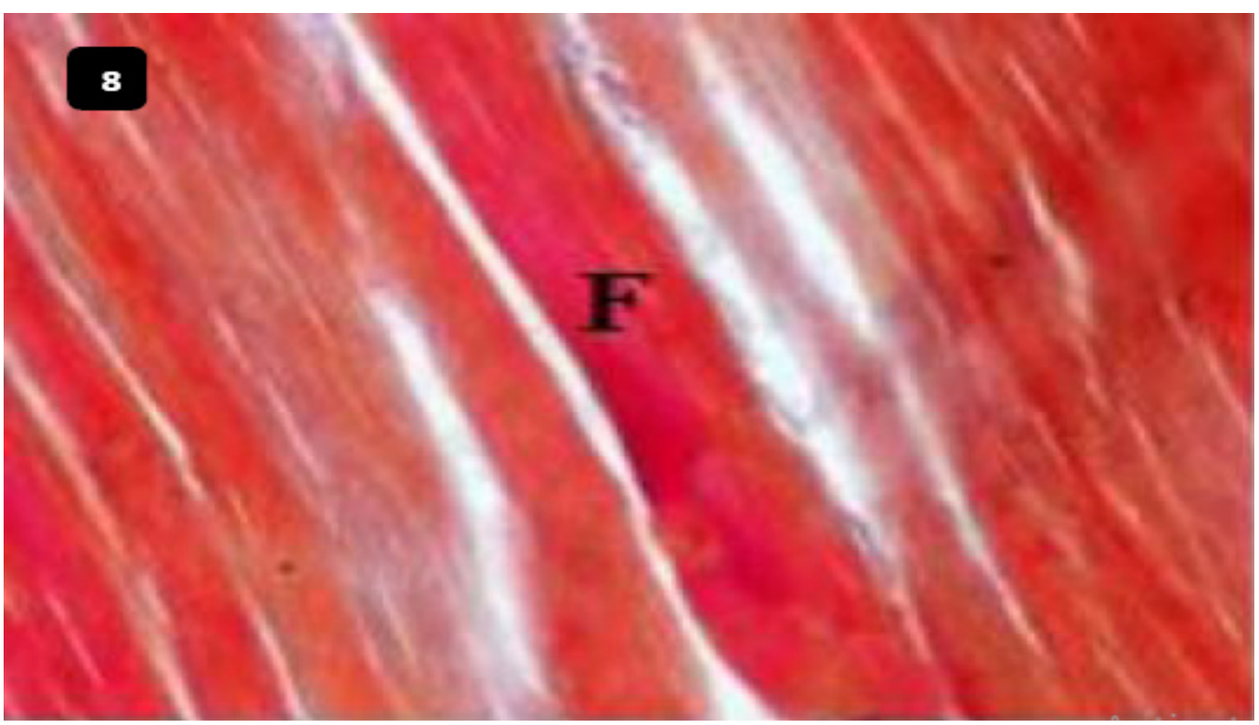

Figure 8: Light micrographs (LM) of a longitudinal section of group IV of EDL muscle of rat revealing the closely typical distribution of collagen fibers surrounding non-branching muscle fibers (F). Masson trichrome ×400.

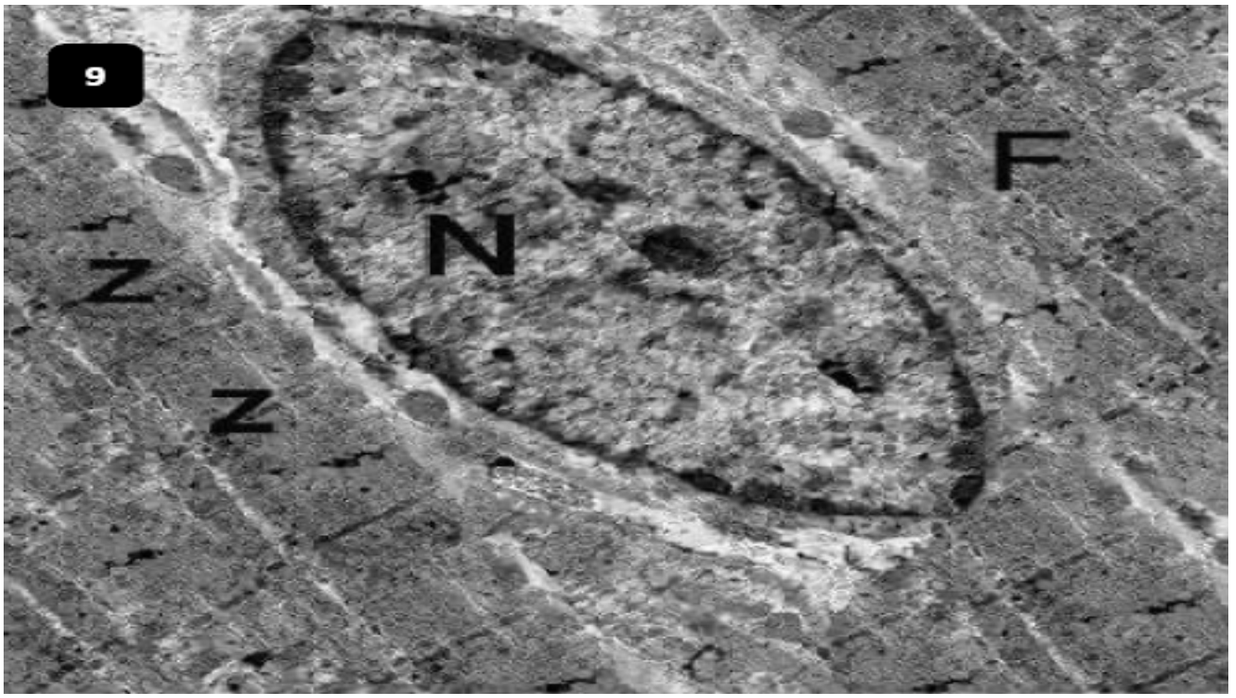

Figure 9: Transmission electron micrographs (TEM) of a longitudinal section in group I of EDL muscle of rat revealing the typical appearance of muscle fibers (F) with dark and light bands. Sarcomeres present in between the two consecutive z lines (z) with oval nucleus (N) and normal mitochondria (m). TEM ×25,000.

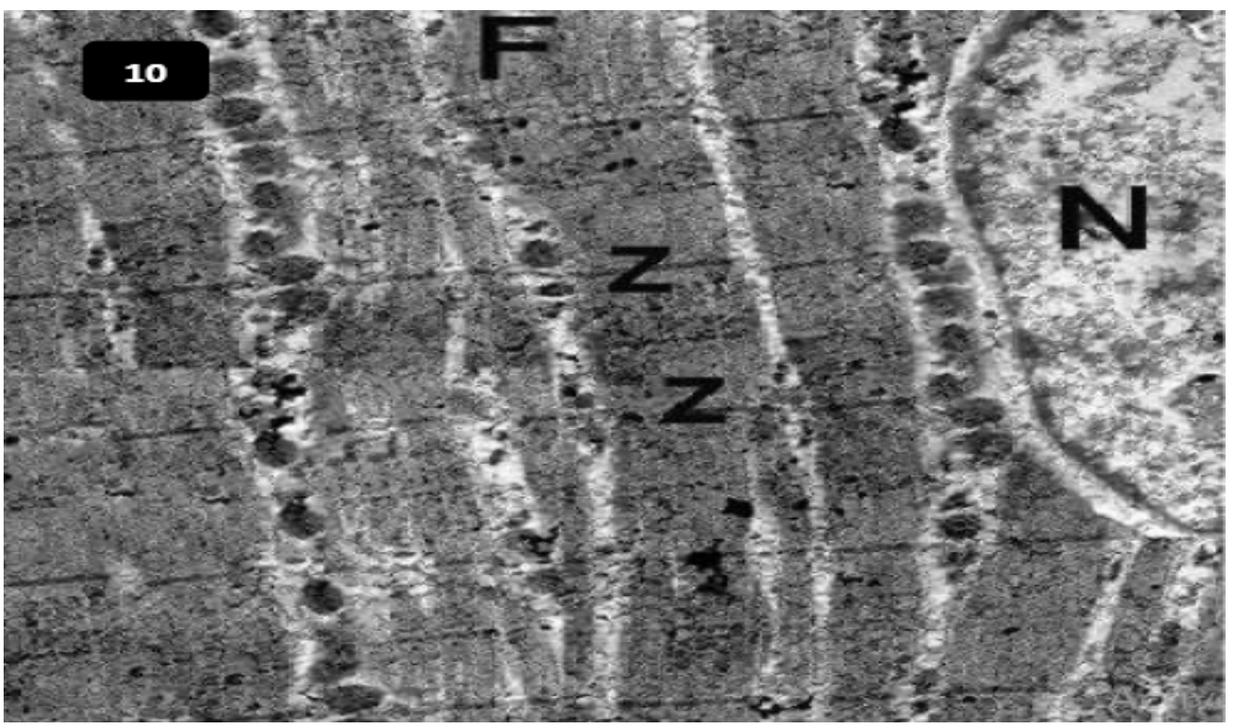

Figure 10: Transmission electron micrographs (TEM) of a longitudinal section in group II of EDL muscle of rats revealing the normal appearance of muscle fiber (F) dark and light strands. Sarcomeres are present in between the 2 z consecutive strands (z) have normal nuclei (N) with normal mitochondria (m). (×25,000).

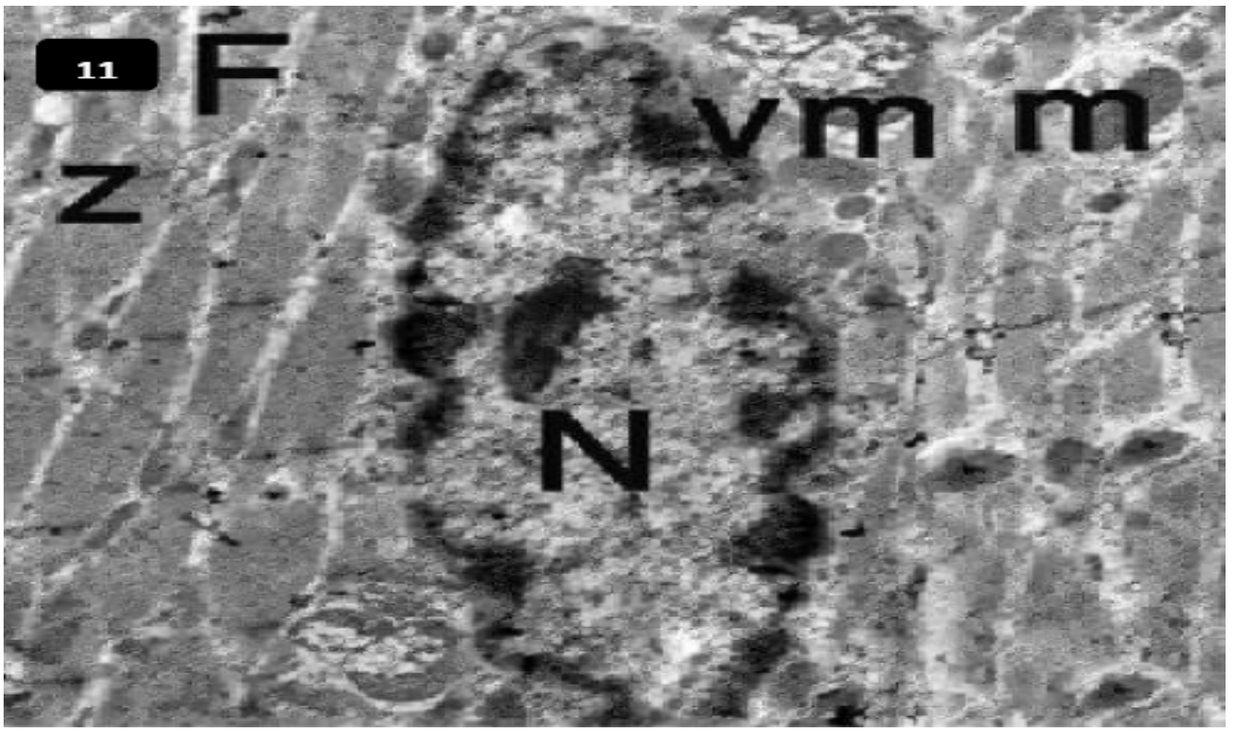

Figure 11: Transmission electron micrographs (TEM) of a longitudinal section in group III of EDL muscle of rat revealing damage with atrophy of nucleus (N) and disorganization and deterioration of myofibrils (F), obvious accumulation, swelling and vacuolation of mitochondria (vm), loss of mitochondrial cristae and electron-dense granules mitochondria (m) and degenerated nuclei (N). Disturbance and loss of Z line. (×25,000).

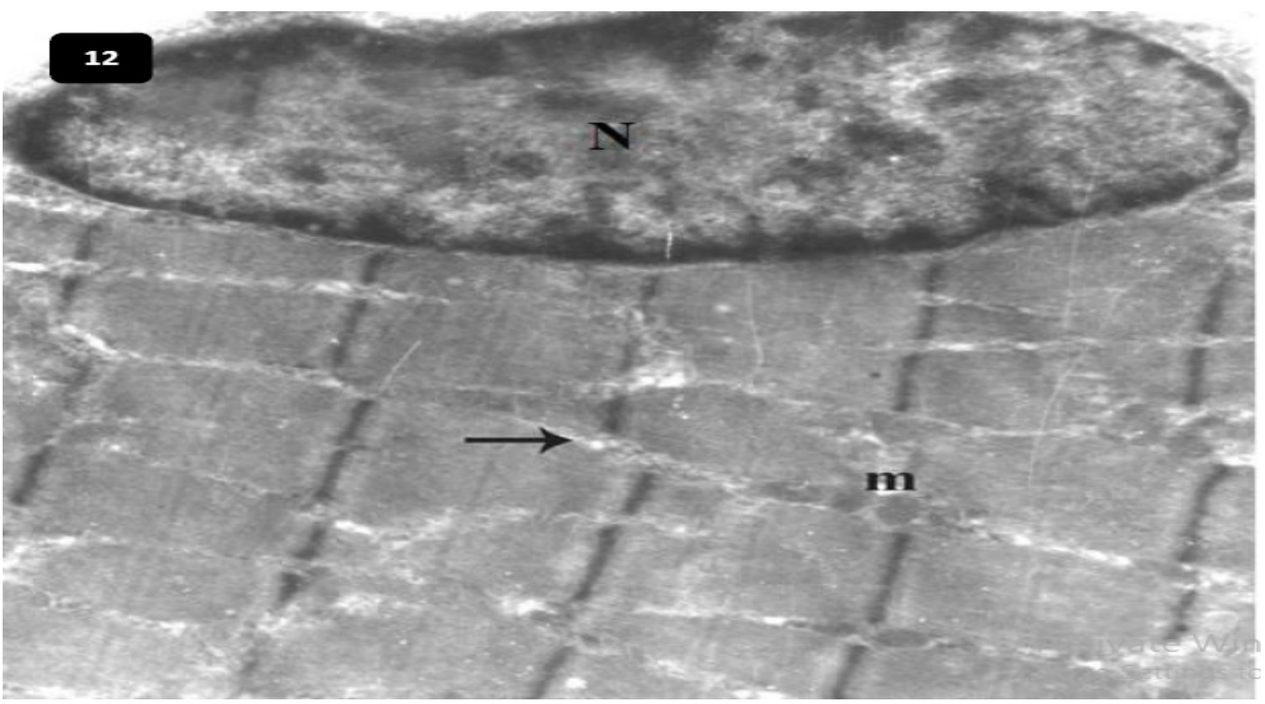

Figure 12: Transmission electron micrographs (TEM) of a longitudinal section through group IV of the rat EDL muscle show a nearly typical view of oval nucleus (N), rows of mitochondria (m) are present among the myofibrilis and the sarcoplasm is filled with myofibrilis parallel to the long axis of the cell and in register with each other t tubules and sarcoplasmic reticulum (arrow).TEM ×25,000.

DISCUSSION

The most common side effect of atorvastatin is myotoxicity that was discovered in recent ages. This work aims to assess the sub-chronic effect of atorvastatin-initiated myotoxicity and evaluate the costus effects upon the protection of muscles against atorvastatin intoxication. Our findings in group III that given atorvastatin revealed a rise of biomarkers of toxicity of muscle fibers, in parallel to the study of El-Ganainy[24] who reported that atorvastatin causing elevation of CPK values was a sign of inflammation of muscle fibers fixed biomarker for myopathy finding in the skeletal muscles as adenosine triphosphate is generated through phosphorylation of adenosine diphosphate as its value increases next to damage to the muscular cellular membrane, with consequent outflow into the bloodstream.

Mahmoud *et al.,* 2019 added that also that troponin 1 and creatinine phosphokinase which are very definite to acute myocardium and myopathy in addition the significant rise in creatinine phosphokinase, dehydrogenation of lactic acid and globin of muscle dependent main the grade of damage in the muscle which causes myopathy and renal disaster resulting in increased values of creatinine and potassium which may also be lead to damage of sodium and K channel causes irretrievable cell injury these results were parallel with our findings[25].

The present work showed a statistically significant reduction in the levels of peroxidase, catalase, superoxide dismutase and glutathione. But the level of malondialdehyde (MDA) is raised in group III received atorvastatin when compared with groups I and III, these findings were in parallel with the results of Bouitbir *et al.,* 2016[26] who found that atorvastatin decreased the levels of catalase, peroxidase, glutathione and superoxide dismutase but increase the level of malondialdehyde (MDA).

The current study showed also that the simultaneous use of costus with atorvastatin produces an obvious enhancement of all biochemical, histopathological and ultrastructural changes. costus is considered an antioxidant factor that controls signs of oxidative stress from atorvastatin in various forms of muscles which parallel with findings of Armelle *et al.,* 2018[27]. Who reported that after treatments with Costus after prevented the effect of streptozotocin by amelioration of normal range of the status of antioxidant of tissue (CAT, SOD, GSH) and the parameters of biochemical of plasma creatinine and urea also ameliorate the histopathological toxicity animal tissue in the group of rats given an overdose of Costus. the extract possesses antioxidant activities responsible for regulating drug tissue damage.

The present study showed that histopathological of the longitudinal section of the muscle of control and costus groups revealed normal structure with normal collagen fiber arrangement in the endomysium surrounding the vascular structures, the findings were parallel to the results of Said *et al*. 2016 who found that the histological structures of control groups showed normal structures of the in the rats[15]. While the present study revealed that the histopathological and ultrastructural damage in the muscles of the third group (atorvastatin only) like myofibrils deterioration, limited injury of myofilaments, also the destruction of sarcoplasm, aggregation of cells, atypical accumulation of mitochondria present below subcell membrane of muscle fiber and between spaces of muscle fibers, mitochondrial vacuolations, nuclei pyknosis and Intense distribution of collagen fibers in the rat muscle of the third group, showed degeneration of fibers and cytoplasm of muscle with, infiltration of cells, intensive nuclei and remnants of nuclei with much collagen fibers surrounded degenerated muscle fibers these results matched those of Said *et al.,* 2016 who reported the rats of atorvastatin only, showed degeneration of fibers of muscles and its cytoplasm with vacuolated mitochondria, degenerated nuclei disrupting intracellular transmembrane vesicle transfer in muscle fibers[15]. Sabine and his colleagues stated that the mechanism of the role of atorvastatin might be related to the term of the gene by reproduction and protein regression by the pathway of proteasome of ubiquitin or because of increase of production of apoptosis decrease in changes chloride channel[5]. Also, Liu *et al.,* 2010 reported that atorvastatin produces a decrease of mevalonate that caused an increase in the production of mitochondrial adenosine triphosphate and oxidative phosphorylation leading to the impairment of metabolism of muscles causing myotoxicity[28]. Furthermore, our results also showed that the longitudinal section of EDL muscle in the rats of group IV, that were given costus root extract with atorvastatin, revealed improvement of damage and regular structure of muscle fibers like groupI. and scarce collagen fibers in the endomysium, these results were in coincidence with Ramya *et al.,* (2015) who hypothesized that costus can lower cardiac enzymes and inflammatory factors, hence reducing muscle injury[29]. Furthermore, the benefits of costus are dependent on its ability to decrease the make of reactive oxygen species (ROS), like phosphorylation of terminal kinase and p38 MAP kinase, as well as its antioxidant effect, which is based on the modulation of peroxidation

of lipid and rise in antioxidant enzymes. activity because it cures reduction of glutathione, these results parallel with results of the present study. In keeping with our findings, Abd El-Rahman 2020 indicated that increases in serum antioxidant effects of costus as well as rises in MMP-13 levels oversee the restoration of normal collagen distribution in the muscles[30].

CONCLUSION

Finally, sub-chronic atorvastatin use can cause myotoxicity, which is characterized by biochemical abnormalities as well as histological and ultrastructural alterations in many types of rat muscles. The antioxidant costus may help to prevent atorvastatin-induced myotoxicity. To confirm our findings, a more human study is needed.

CONFLICT OF INTEREST

There is no potential conflict of interest among the authors.

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الملخص العربي

القسط يحسن السمية العضلية الناجمة عن أتورفاستاتين في الفئران: الدراسات التشريحية المرضية والبنية التحتية والكيمياء الحيوية

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الخلفية: فرط شحميات الدم هو السبب الرئيسي للسكتة القلبية والوفاة. أتورفاستاتين هو أفضل دواء لعلاجه. زيادة استخدامه أدت إلى ظهور آثار جانبية وخاصة العضلات. القسط هو عشب طبي يمنع مخاطر التسمم التي تحدث بسبب استخدام أتورفاستاتين. الهدف من هذه الدراسة هو تقييم مستخلص القسط ضد السمية العضلية للأتورفاستاتين في ذكور الجرذان البيضاء.

الطريقة: تم استخدام ثمانين فأرا ألبينو بالغين، مقسمة إلى أربع مجموعات كل مجموعة عشرين فأرًا، المجموعة الأولى كمجموعة ضابطة، أعطيت الماء فقط طوال التجربة. المجموعة الثانية أعطيت مستخلص جذور القسط بجرعة (0.4 ملغم/كغم) يومياً. أعطيت المجموعة الثالثة 50 ملجم/كجم/يوم من أتورفاستاتين المسال في ماء نقي والمجموعة الرابعة أعطيت خلاصة جذر القسط بجرعة (0.4 ملجم/كجم) يومياً بجرعة 50 ملجم/كجم/يوم. يتم تسييل أتورفاستاتين في الماء النقي يوميًا لمدة 90 يومًا عبر أنبوب معدي.

بعد انتهاء التجربة، تم تخدير الفئران واستئصال الباسطة الطويلة للأصابع ثم تقييم التشريح المرضي للعضلات بواسطة المجاهر الضوئية والإلكترونية وتقييم إنزيمات القلب في الدم والبوتاسيوم والكرياتينين والمصل (CPK).

النتائج: شذوذات كبيرة في جميع المؤشرات الحيوية لسمية العضلات مع تغيراتها التنكسية، واستخدام مستخلص جذر القسط مع تناول أتورفاستاتين شبه المزمن لتخفيف علامات سمية العضلات.

الخلاصة: الاستخدام شبه المزمن للأتورفاستاتين يمكن أن يسبب السمية العضلية. على العكس من ذلك، قد يساعد القسط المضاد للأكسدة على منع السمية العضلية الناجمة عن أتورفاستاتين.

الكلمات المفتاحية: مستخلص جذر القسط؛ أتورفاستاتين. السمية العضلية. التشريح المرضي البيوكيميائي؛ البنية التحتية.