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RESEARCH ARTICLE

Neuroprotective effects of cobalt ferrite nanoparticles coated with *sumac* on damaged sciatic nerve recovery

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ABSTRACT

Objective(s): Although damaged peripheral nerves have the ability to repair, axon regeneration proceeds slowly and often poor functional results are observed. Many methods are used to repair peripheral nerve lesions, but very few have demonstrated clinical success. Hence, the intention of the present study was to explore the regenerative outcomes of cobalt ferrite nanoparticles coated with *sumac* on rat sciatic nerve injury.

Methods: Forty male Wistar rats were separated into four groups: the sham group (surgery without damage to the nerve), the negative control (nerve compression without nanoparticle injection), the experimental group 1 (nerve compression given 10 mg/kg dose of drug), and the experimental group 2 (nerve compression given 20 mg/kg dose of drug). The sciatic nerve was then compressed one centimeter above the point where it splits into three branches, tissue and muscle sections were examined in addition to foot print and hot plate tests.

Results: When compared to the negative control group, the speed of recovery and restoration of sensory and motor neuron function was significantly faster in groups treated with cobalt ferrite nanoparticles coated with *sumac*.

Conclusions: Injection of cobalt ferrite nanoparticle coated with sumac increases the speed of repair of peripheral nerve damage in rats.

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INTRODUCTION

The most frequent cause of nerve damage is the injury of peripheral nervous system [1]. Despite the ability of damaged peripheral nerves to regenerate, axon regeneration is slow and frequently results in subpar functional outcomes [1]. The ultimate goal of peripheral nerve repair strategies is to achieve maximum functional efficiency and shorten the recovery period [2]. Current methods for peripheral nerve regeneration include self-healing, surgical treatment, and physiotherapy. These methods are usually combined with other therapies to focus on reducing pain and increasing nerve regeneration in patients [3]. Speed of nerve repair following injury is essential to improve motor function and tissue re-denervation. Therefore, any factor that increases the growth rate of axons and causes tissue re-denervation could be useful in the process of nerve repair and recovery of motor function [4].

Rhus coriaria Linn. (Anacardiacea), more commonly referred to *sumac*, is a spice, condiment, and flavoring that is commonly used, especially in the Mediterranean region. *Sumac*, because of its powerful antioxidant capacity, has been used for the management and treatment of many diseases [5]. In this regard, Khalilpour and his colleagues showed that treatment with *sumac* extract following optic nerve damage had an 84.87 percent prevention of ischemia as measured by fluorescence molecular

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tomography (FMT) imaging [6]. In a different study, *Rhus coriaria L.* was found to inhibit the production of the pro-inflammatory mediator IL-8 in HaCaT cells, raising the possibility that it might be used to treat skin inflammation [7]. Also, *sumac* extract has been shown to speed up wound closure in rats after wound injury [8]. Studying neuroprotective effects of different sumac extracts in combination with their antimicrobial and antioxidant properties demonstrated that water, methanol, and n-hexane extracts of sumac caused neuroprotective effect through cholinesterase inhibitory activity against acetylcolinesterase (AChE) and butyrylcolinesterase (BChE). The results argued that neuroprotective impact of sumac in neurodegenerative disease is related to its antioxidant activity [9]. Furthermore, neuro-inflammatory effects of ethanolic extract of sumac was observed by reducing reactive oxygen species and nitric oxide, TNFα, iNOS, and COX-2 mRNA level; inhibiting NFκβ pathway; and increasing IL-10 levels [10]. In vivo study of neuroprotective activity of sumac on neuronal ischemic injury model showed that phenolic components, especially linoleic acid, have anti-inflammatory effects responsible for neurodegenerative diseases treatment [11].

Nanotechnology has emerged as an interdisciplinary, independent, and attractive field of research. Applications of nanoparticles (NPs) in the biomedical sciences have provided new ways to treat diseases [12]. Unlike conventional systems such as tablets and solutions, NPs intelligently control and perpetuate drug distribution in different parts, making them more effective [13]. Among NPs, magnetic NPs have unique physical and chemical properties which have been of great interest in medical and biomedical applications [14]. In this regard, the present study aim to use $CoFe_2O_4$ NPs as a carrier, coated with *sumac* to facilitate therapeutic agent delivery and absorption into the damaged nerves. Covering NPs used in medical treatments is due to several reasons, including reducing degradability, toxicity and prevent aggregation, increased dispersion, and thermal stability [15]. The current study's objective was to assess the neuroprotective properties of $CoFe_2O_4$ NPs coated with sumac on damaged sciatic nerve recovery.

MATERIALS AND METHODS

Synthesis of $CoFe_2O_4$ sumac NPs

At First**,** 2 g of *sumac* powder was added to the 100 ml deionized water at 80 °C and stirred for 50 min. After cooling at room temperature, solution was centrifuged three times and the approximately red color supernatant was separated and added to the cobalt ferrite NPs that synthesized by co-precipitation method and stirred for one hour at 40 °C. Finally, the *sumac* coated NPs were dried at oven at 50 °C for 12 hours.

Characterization of $CoFe_2O_4$ NPs

The synthesized NPs were characterized by Vibrating Sample Magnetometer (VSM) (Meghnatis Daghigh Kavir Co., Iran), Scanning Electron Microscopy (SEM), and Transmittance Electron Microscopy (TEM) (Philips CM10).

Animals

For the present experiment, 40 male Wistar rats weighing 250-300 g were used. Animals had free access to water and food at room temperature of 22± 2 °C. The room light was set to 12-h light/dark cycle. The following groups of animals were chosen at random: Sham operated group (only surgery without nerve damage); Negative control group (sciatic nerve crush without treatment); Experimental group 1 (sciatic nerve crush and treatment with 10 mg/kg doses of cobalt ferrite NPs coated with *sumac*); Experimental group 2 (sciatica nerve crush and treatment with 20 mg/kg doses of cobalt ferrite NPs coated with *sumac.* Experiments were conducted in accordance with the laboratory ethics of University of Mohaghegh Ardabili, (ID code: IR.ARUMS.REC.1400.083).

Surgical Procedures

The animals were anesthetized using ketamine and xylezine. Then, the thigh hair was shaved with a razor. The area was disinfected with alcohol and betadine, the muscle layer was cut, the sciatic nerve was exposed, and a piece was crushed from above the site of the nerve bifurcation with a surgical forceps. The fascia, skin, and muscle layer were then stitched together. Following the procedure, each rats was housed in a individual cage to prevent them from injuring one another. For a week, betadine was used to clean the surgical site and prevent infection. Additionally, 1 mg/kg of buprenorphine was used to lessen the pain for 3 days.

Walking Tract Analysis

The sciatic function index (SFI) was used to determine whether nerve function had improved.

Fig. 1. Procedure of animal modelling

In short, the test was done in a corridor with dimensions of (10× 25 × 100 cm) with enclosed and dark room. The hind feet of rats were immersed in pigment before being placed at the entrance to the corridor to walk on the white paper that had already been laid out on the floor. Then, three of the rats' footprints on the white paper were recorded, and the sciatic function index was subsequently obtained by entering the information from test into the subsequent equation.

SFI = -38.3[(EPL-NPL)/NPL] + 109.5[(ETS-NTS)/NTS] + 13.3 [(EIT-NIT)/NIT]-8.8

The length of the foot is denoted by PL in the formula aforementioned, the distance between the animal's second and fourth toes is denoted by IT, and the distance between its first and fifth toes is denoted by TS. In addition, the letter N stands for a sound foot, while the letter E stands for a foot that has undergone surgery.

Hot Plate Evaluation

The hot plate evaluation was performed to evaluate the functional restoration of sensory neurons as well as the possibility of thermal hyperalgesia. In the present test, the operated animal foot was placed on the metal surface heated to 54 ± 1 °C, and the animal's reaction to pain was measured by lifting its foot off the hot plate. Three times, at 2 min intervals, the average time was obtained, and the results were recorded. The cut-off time for the present test was 12 seconds in order to protect animal tissues

Histomorphometric Evaluation

After identifying the sciatic nerve and anesthetizing the animals, a section below the nerve crush site was taken from each group and fixed in 2.5% glutaraldehyde at the final stage of the experiment. The following step involved dehydrating tissue samples in ethanol, using resin to embed them, and cutting them into semi-thin (1 mm) sections that were colored with toluidine blue (1%) for light microscopic analysis. The Image J software was used to calculate the number of nerve fibers, fiber diameter, number of myelin fibers, and thickness of the myelin sheath.

Histological evaluation of gastrocnemius muscle

Evaluation of histological changes in the gastrocnemius muscle was conducted through preparing tissue sections from the middle part of the muscle ventricle and stained with Masson Trichrome staining. Subsequently using light microscopy, the existence of fibrous connective tissue was investigated between muscle fibers.

Muscle mass ratio evaluation

The left and right gastrocnemius muscles in each group were painstakingly dissected from the tendon, bone and precisely weighed. The weight of the healthy leg muscle to that of the operated leg muscle was then used to calculate the gastrocnemius muscle weight constant for each rat.

Statistical analysis

The results were analyzed using SPSS software and one-way analysis of variance (ANOVA). The

presence or absence of statistically significant variations between different groups was determined by Tukey post-hoc test. $P \leq 0.05$ was considered statistically significant.

RESULTS

Characterization of NPs

SEM and TEM Images

Figure (a) shows the SEM image of ferrite NPs coated with *sumac*. It seems that particles have no specific shape whit nearly uniform size distribution under 200 nm. Figure (b) shows the TEM image of the $CoFe_2O_4$*sumac* NPs (Fig. 1). According to the TEM image the size of NPs is under 50 nm approximately, and some agglomeration is observed due to the magnetic nature of ferrite NPs. Image contains the dark pasurts which are particles together the bright thin layers which coated them as *sumac* shell.

Vibrating Sample Magnetometer (VSM) characterization

The magnetic hysteresis loop of the *sumac* coated cobalt ferrite NPs which obtained at the 10KOe applied magnetic field presented at Figure (3). The saturation magnetization and coercive field of the NPs are 22.6emu/g and 650 Oe respectively. It is lower than the bare $CoFe_2O_4$ NPs due to the *sumac* shell coated the surface of particles effectively.

XRD analyze

The diffraction peaks which were produced in the crystal plane directions 220, 311, 400, 511 and 440, indicate the creation of a structure that is cubic and are consistent with the typical cobalt ferrite diffraction pattern (Fig. 4). The broadening caused by the diffraction peaks suggests that the size of the synthesized nanoparticles has decreased. The average size of synthesized crystals was 23 nm. The Debye-Scherr equation was used to calculate their size.

$$D = 0.9\lambda / \beta Cos\theta$$

The main diffraction peak's full width at half maximum (β), the wavelength of $CoFe_2O_4$ (λ), and the diffraction angle (θ) are included in this equation. The uncoated cobalt ferrite sample has a lattice constant of 391.8 angstroms and the sumac coated sample has a lattice constant of 8.357 angstroms.

FTIR analyze

The FT-IR spectrum of sumac and nanoparticles coated with sumac is shown in Figure 5. The vibration of stretching of the H-O band is associated with the absorption band generated at 3397 cm^{-1}. The CH- and CH2- hydrocarbon bands vibration has led to the creation of an absorption band at

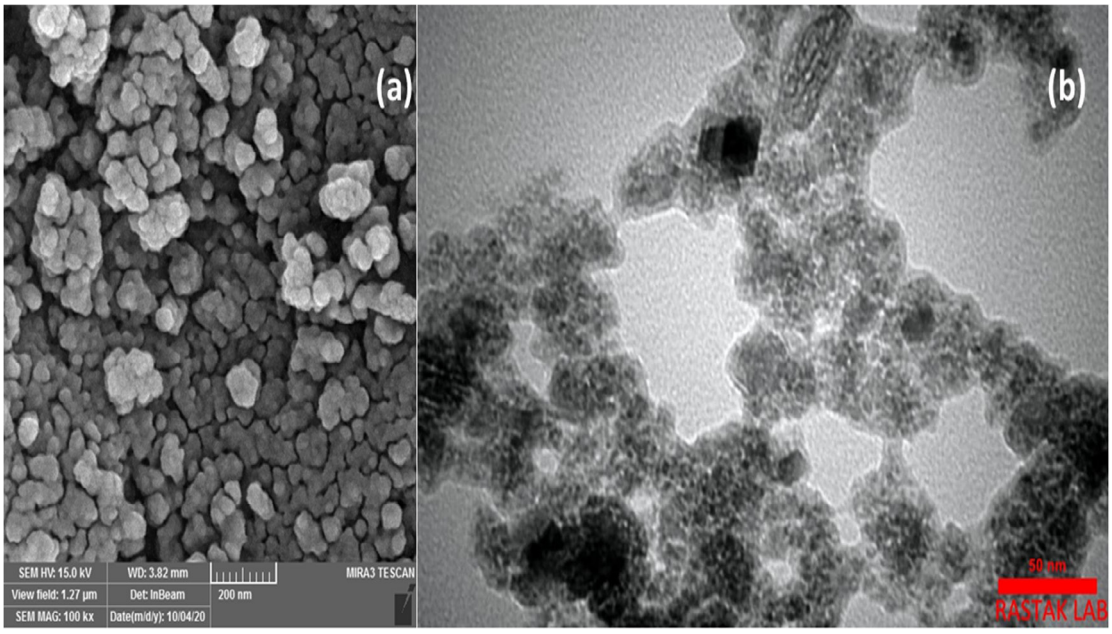

Fig 2. (a) SEM image of nanoparticles, (b) TEM image of nanoparticles

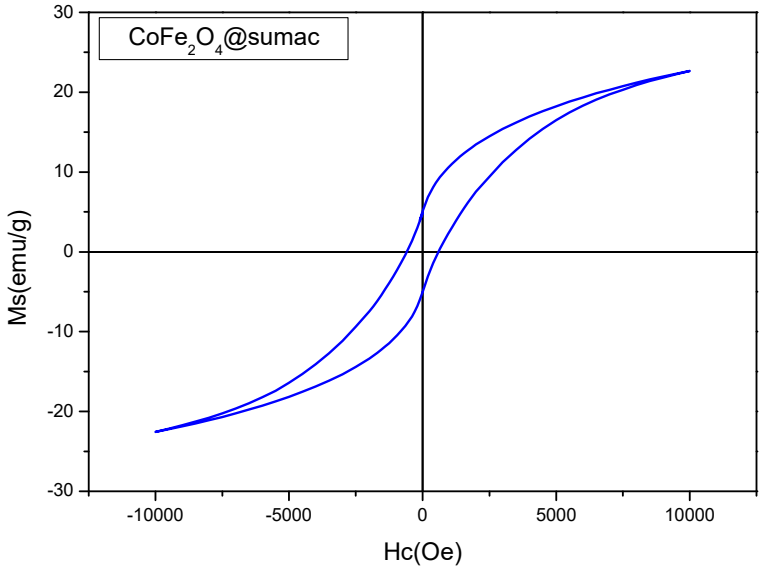

Fig. 3. Investigation of *Vibrating Sample Magnetometer (VSM)* characterization of SU$CoFe_2O_4$ nanoparticles

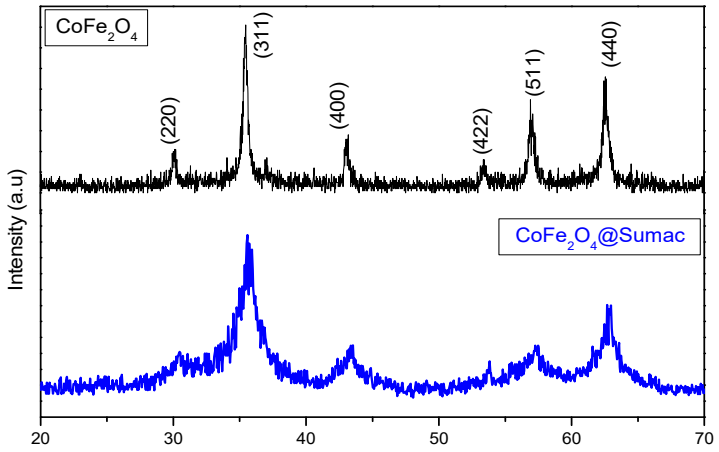

Fig. 4. XRD pattern of $CoFe_2O_4$synthesized using extract and $CoFe_2O_4$ nanoparticles

2343 cm-1. The vibrational band caused by the C=O carbonyl group is observed at 1652 cm^{-1}. Regarding the spectrum of cobalt ferrite nanoparticles coated with sumac, several important absorption bands could be mentioned at 425 and 601cm^{-1}, which are related to the vibrations of metal ion bands with oxygen in Fe-O and Co-O. On the other hand, the vibrational band related to the carbonyl group has shifted to lower frequencies, and the vibrational bands caused by the hydrocarbon can also be seen, which confirms the formation of nanoparticles using the extract.

Motor function evaluation

The rate of motor function recovery was assessed by measuring the sciatic nerve function index (SFI) in all groups. The SFI value in the 2nd week after sciatic nerve crush decreased to the lowest level in all experimental groups (Fig. 6). Then in weeks 4, 6, and 8, the SFI index in the experimental groups treated with cobalt ferrite covered with *sumac* at a dose of 20 mg/kg showed the highest improvement in motor function compared to the other groups (P≤0.05; Fig. 6). The motor function index significantly improved in the experimental group given cobalt ferrite covered

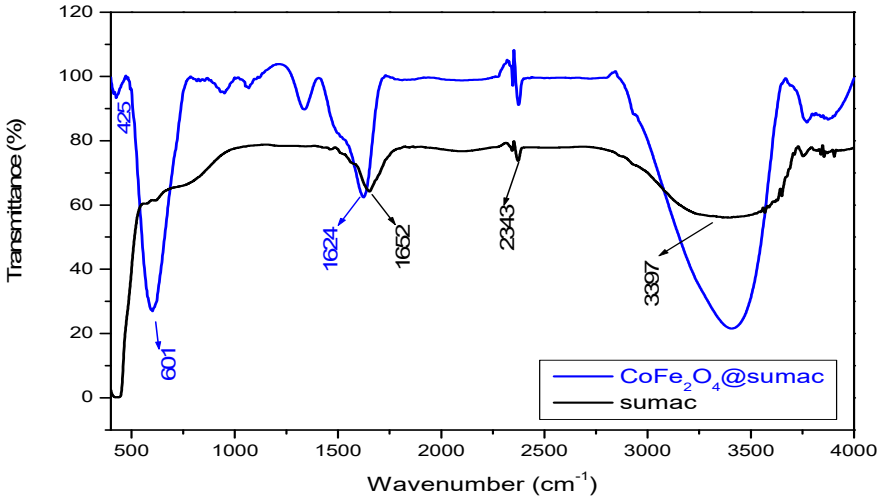

Fig. 5. FT-IR spectrum of sumac and cobalt ferrite sample coated with sumac

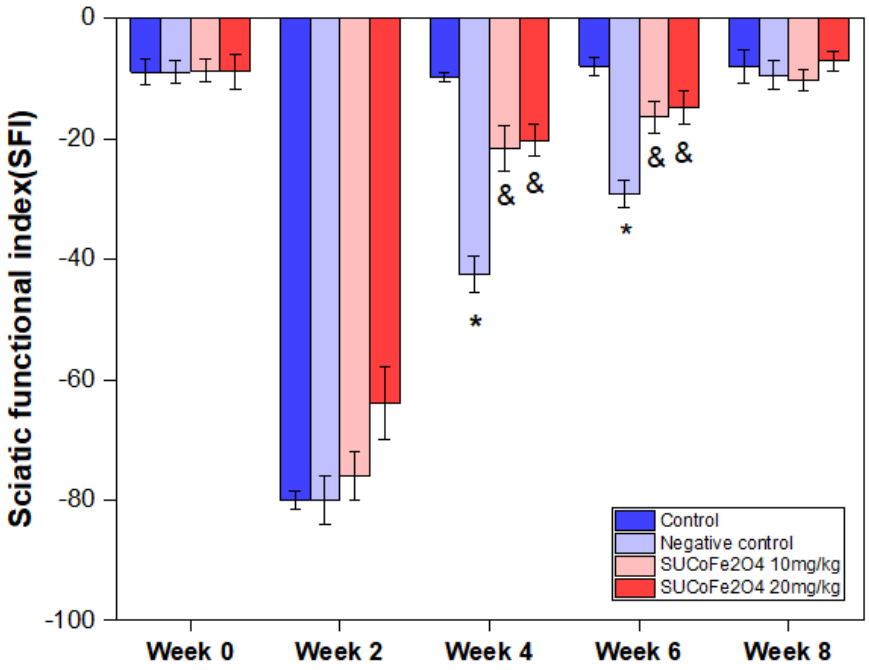

Fig. 6. Sciatica performance index evaluation (SFI). SFI was assessed in all groups at 2, 4, 6, and 8 weeks following surgery. The data are shown as mean ±SEM (P 0.05). *: in comparison to the control; &: in comparison to the negative group

with sumac at a dose of 10 mg/kg compared to the negative control group. In comparison to the other groups, the negative control group had the lowest level of SFI at week 8, but overall there was no statistically significant distinction between the groups (Fig. 6).

Evaluation of sensory neuron recovery

As shown in Figure 7, the results of the hot plate test revealed that there was not a noticeable distinction between the groups prior to sciatic nerve crush. Data analysis from 2, 4, 6, and 8 weeks after nerve compression indicated that sensory function was significantly improved in the groups treated with cobalt ferrite nanoparticles coated with sumac as compared to the negative control group (P≤0.05).

Histomorphometric evaluation

The results of histomorphometric factors of the

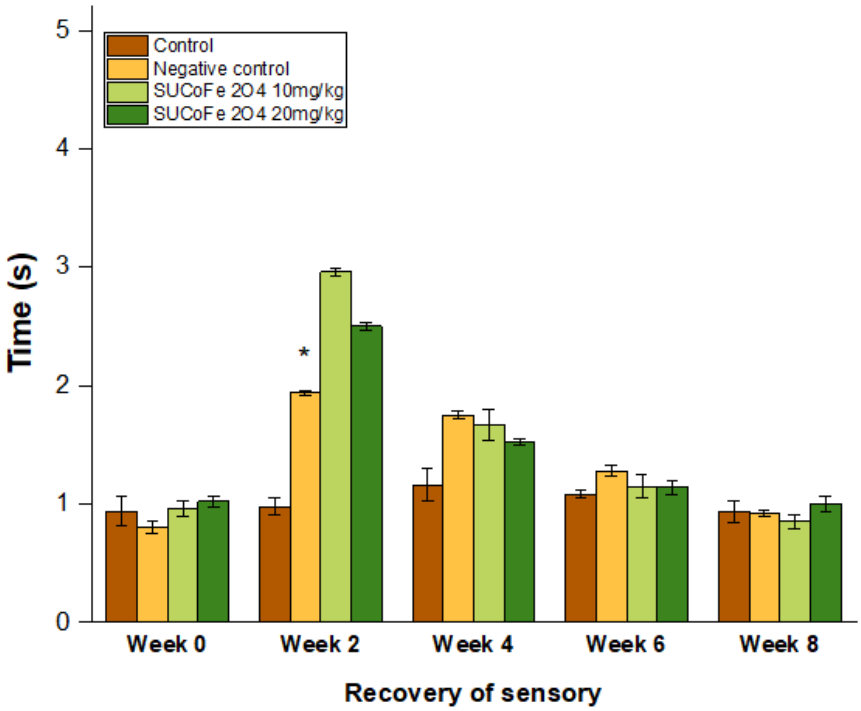

Fig. 7. Evaluation of sensory neuron recovery. All groups underwent the hot plate test at 2, 4, 6, and 8 weeks following surgery. The data are presented as mean ± SEM, (P≤0.05). *: in comparison to the control

Table 1. Morphometric analyses of the distal part of the nerve in the 8th week following surgery

Groups	Number of Fibers	Diameter of Fibers (µm)	Diameter of Axons (µm)	Myelin Sheath Thickness (µm)
Control	**5582± 2/18**	**5.62± 0/41**	**4,31± 0/03**	**1.31± 0/21**
Negative control	**6941± 4/7***	**2.71± 0/19***	**1.92± 0/1***	**0.79± 0/11***
$SUCoFe_2O_4$10mg/kg	**7141± 11/2**	**3.82± 0/41**	**2.91± 0/22**	**0.91± 0/21**
$SUCoFe_2O_4$20mg/kg	**7381± 15/1&**	**4.85± 0/33&**	**3.66± 0/17&**	**1.19± 0/22&**

distal nerve segment for all experimental groups at week 8 are displayed in Table 1. In groups treated with cobalt ferrite nanoparticles coated with *sumac*, number of fibers, fiber diameter, axon diameter and myelin sheath thickness were considerably higher than the untreated control group, according to the results of morphometric studies (P≤0.05; Table 1).

Histological evaluation

Sections of the gastrocnemius muscle were colored with Masson trichrome to determine the degree of muscle atrophy. The findings showed that there was less muscle damage in the groups treated with cobalt ferrite nanoparticles coated with sumac than in the negative control group. More fibrous tissue developed in the negative control group than in the other groups, which suggests the more destruction of the muscle (Fig. 8).

Muscle mass ratio

The muscle mass ratio in the negative control group was significantly lower in comparison to the control (P≤0.05; Fig. 9). Also, muscle mass ratio in both groups treated with cobalt ferrite nanoparticles coated with *sumac* (10 or 20 mg/kg) notably increased compared to the negative control (P ≤ 0.05; Fig. 9).

DISCUSSION

Peripheral nerve injuries are common and frequently result in long-term neurological dysfunction without effective treatments [16, 17]. Due to ineffective and sluggish axonal regeneration, these lesions typically result in a partial or complete

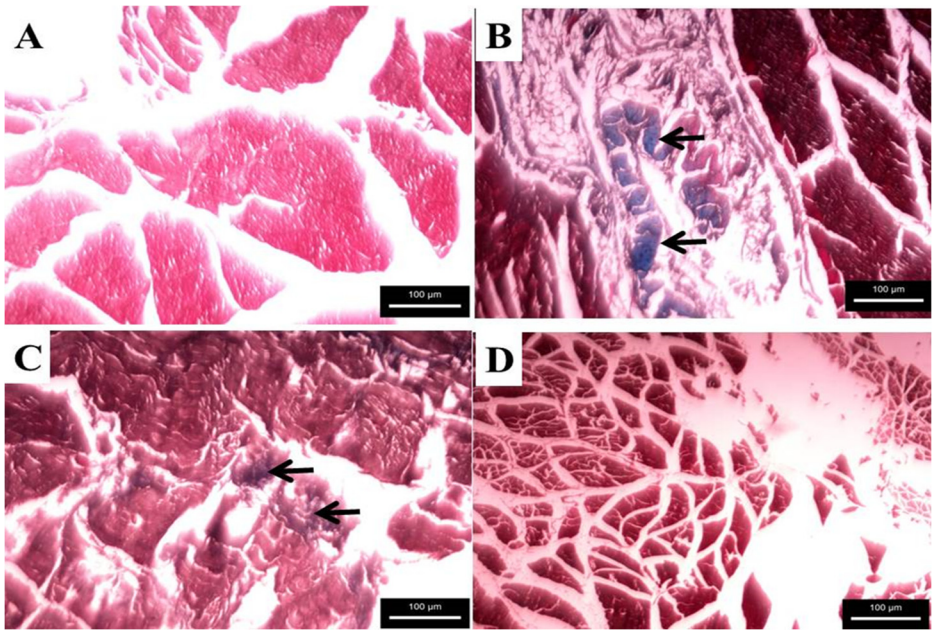

Fig. 8. Images of nerve sections stained with Masson trichrome. In this picture, (A) shows the sham group, (B) the negative control group, (C) treatment group 1 given 10 mg/kg dose of cobalt ferrite nanoparticles coated with *sumac*, (D) treatment group 2 given 20 mg/kg dose of cobalt ferrite nanoparticles coated with *sumac*.

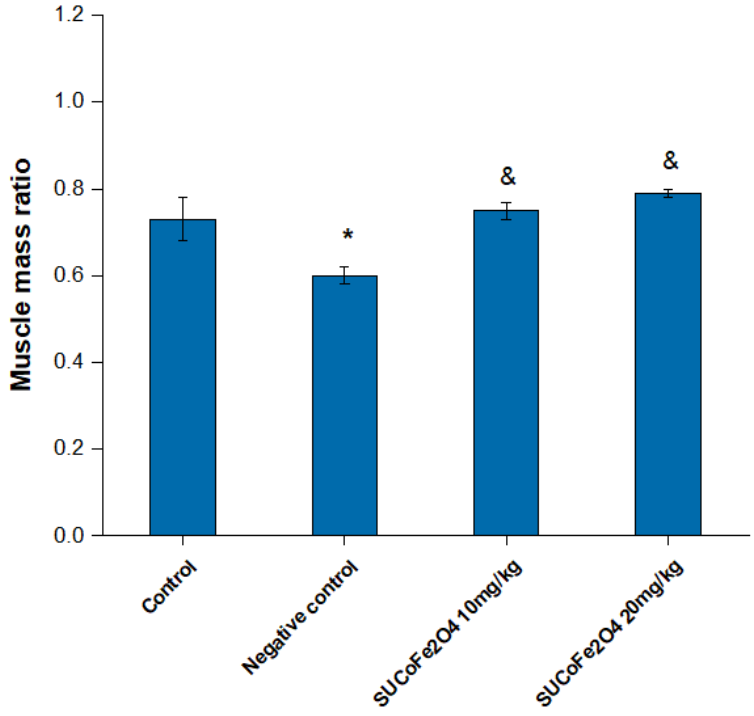

Fig. 9. The muscle mass ratio of four groups at 8 weeks after surgical operation. The data are demonstrated as mean ± SEM (P≤0.05). *: in comparison to the control group, &: in comparison to the control negative group

loss of sensory, motor, and autonomic functioning [18, 19]. Drug therapy is a potential option for treating nerve injuries. It has been shown that the use of drugs which improve neurotrophic and growth factors synthesis has important effects on nerve regeneration [20].

Sumac, Mediterranean flavoring agent, has various therapeutic activities, such as anticancer, antimicrobial, antioxidant, anti-ischemic, cardioprotective, neuroprotective, hepatoprotective, and anti-inflammatory effects [21]. Pharmacological properties of sumac are due to the existence of different components, e.g., tannins, phenolic acids, gallic acids, tannins, anthocyanins, myricitrin, apigenin, and luteolin [22]. Previous studies have shown that the antioxidative and anti-inflammatory mechanisms of sumac extracts are able to exert neuroprotective effects.

Gallic acid, as a phenolic acid derivative in sumac, has shown antioxidant effects through suppression of reactive oxygen and nitrogen species by electron transfer and anti-inflammatory activities by inhibiting pro-inflammatory cytokines, chemokines and increasing an important immunoregulator protein called HSP-70, in sciatic nerve damage rats [23]. Furthermore, studying neuroprotective effect of gallic acid was conducted by oral administration of it to sciatic nerve crush rats with different doses for 21 days. The results showed the improvement of motor coordination and sciatic nerve conduction velocity. Reduction of oxidative stress, superoxide dismutase and suppression of mitogen-activated protein kinase (MAPK) are possible mechanisms underlying the neuroprotective effect of gallic acid in functional improvement of sciatic nerve injury models [24]. Antioxidant capacity of sumac in type 2 diabetic patients was determined via significant increase in total antioxidant capacity (TAC) in comparison with baseline. It has been demonstrated that gallic acid and tannin are two main components of sumac responsible for its antioxidant ability [25]. The mechanism underlying alleviating neuropathic pain via gallic acid was investigated in a chronic constriction injury model treating with gallic acid for one week. Based on previous study, it has been shown that gallic acid could reduce neuropathic pain by suppressing the P2X7 receptor, TNF-α, and NF-κB/STAT3 signaling pathway [26]. Different extracts of sumac, including aqueous, ethanolic, methanolic, hydroalcoholic, n-hexane, or acetone extracts have displayed antioxidant activity [5]. Aqueous extract of sumac demonstrated antioxidant activity in rats [28-30].

Many current treatment approaches could be made significantly more effective by the use of NPs in medicine. Combining drugs with NPs could improve their ability to selectively accumulate in diseased tissues and cross cell membranes [28]. The use of nanotechnology to synthesize neuroprotective drugs by promoting neuronal survival, axonal sprouting, and the reinnervation of target tissues, can increase the effectiveness of pharmacotherapy [31]. Application of cobalt ferrite nanoparticles (CFNs) in the field of medical research is due to their numerous benefits, such as low toxicity, adjustable size, simplicity of surface processing, chemical stability, high permeability, antimicrobial, anticancer, and antioxidant effects [32]. Several previous studies have investigated the antioxidant activity of CFN which is important for neuroprotection effects. Jnanranjan et al. found out that hydrothermally synthesized CFNs display free radical scavenging activity [33]. Furthermore, it has been demonstred that as the concentration of CFN increases, its antioxidant effects become higher [34-36].

The findings of the functional tests, morphological and histological investigations indicate the positive effect of cobalt ferrite NPs coated with *sumac* on the healing process of the sciatic nerve injury. In such a way that the examination of recovery of motor performance by analyzing the data of the walking track test showed that the performance improvement in the experimental group 2 was significant, but the improvement rate was not significant in the experimental group 1. Sensory functional recovery was evaluated by the hot plate test, which showed a better improvement in the groups treated with cobalt ferrite NPs coated with *sumac* compared to the negative control and sham groups. By examining the muscles of the gastrocnemius on the treated and healthy sides, different degrees of muscle atrophy were determined in the muscle on the operated side with the naked eye and also by examining the weight of the muscles. The amount of atrophy was significant in experimental group 2, which received a larger amount of cobalt ferrite NPs coated with 20 mg/kg of *sumac*, but it was not significant in experimental group 1, which received a lower concentration of this NPs. To check the severity of muscle atrophy, Masson's trichrome staining was used, and it was

found that in the group treated with cobalt ferrite covered with *sumac*, there was less improvement in muscle volume and less muscle destruction than the control group. The histomorphometric studies showed that the morphometric factors increased in the experimental groups treated with NPs compared to the negative control group. According to the results of the present research, cobalt ferrite NPs covered with *sumac*, may exert a positive effect on the process of regeneration and restoration of the damaged sciatic nerve.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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