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An investigation of synergistic effects of cerium oxide nanoparticles and eugenol on the recovery of sciatic nerve in rat model

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Introduction

Sciatica is often associated with leg pain. This disease is caused by inflammation or compression of the lumbosacral nerve roots (L4-S1) that form the sciatic nerve. In a study, it has been reported that about 60% of patients with back pain and leg pain are clinically diagnosed with sciatica (1). If there is a history of leg pain, back pain or pain below the knee, sciatica should be suspected. There are also symptoms such as tingling, numbness or muscle weakness in the legs (2). Sciatica may start suddenly with physical activity. If nerve root pain extends below the knee, its origin is consistent with spinal cord injury. The use of non-steroidal anti-inflammatory drugs may provide short-term relief for back pain and sciatica. However, in some cases, surgery is considered as an option for sciatica treatment (3,4).
Nowadays, the use of nanomedicines to treat many diseases has attracted the attention of many researchers. Nanomedicines are very useful in the field of medicine due to their small size and targeted delivery to the target tissue (6). Cerium oxide nanoparticles have strong antioxidant properties in inhibiting free radicals. (7). Eugenol is a biologically active compound that has many biological benefits such as antioxidant, neuroprotective, anticancer, antibacterial, antifungal and insecticidal activities (8). In this study, the neuroprotective potential of eugenol/cerium oxide in the recovery of the sciatic nerve was investigated in the rat model.

Materials & Methods

Male rats weighing 250-300 g were divided into four groups (n=7). Control group and sciatica model received saline. One group (50 mg/kg eugenol/20 mg/kg cerium oxide nanoparticles) and the other group (100 mg/kg eugenol/20 mg/kg cerium oxide nanoparticles) were injected intraperitoneally for one week. The sciatic nerve was revealed by splitting the muscle layer. For model sciatic nerve injury, a piece of nerve was compressed above the trifurcation. Buprenorphine (1mg/kg) was injected for two days after surgery to reduce pain. All groups were evaluated by “Walking Track” test twice a week. The hind paws of the animal were painted with ink. Then, the footprints of the rats were recorded to determine the Sciatic Function Index (SFI). To evaluate the thermal pain threshold and the degree of functional recovery of sensory neurons, the hot plate test was performed. So that the rats were placed separately on the hot plate of 52 ± 1 °C. Response latencies were recorded as hind paw jumps. At the end of the eighth week, the gastrocnemius muscle of the right leg (operated) and the left leg (healthy) were

separated. Then the weight of the gastrocnemius muscle was weighed. The resulting data were analyzed using SPSS software and one-way ANOVA.

Results & discussion

The resulting data showed that in all groups, improvement was observed from the second week. In the groups treated with eugenol/cerium oxide, the improvement of sensory function was better than the control group, and finally, the highest improvement of sensory function at the end of week 8 in both groups receiving mg/kg (50 eugenol/20 mg/kg cerium oxide) and mg/kg (100 mg/kg eugenol/20 mg/kg cerium oxide) compared to the negative control ($p<0.05$). However, at the end of week 8 in rats receiving (100 mg/kg eugenol/20 mg/kg cerium oxide) compared to the negative control, the recovery of Sciatic Function Index (SFI) was significant ($p<0.05$). Also, the injection of eugenol/cerium oxide nanoparticles increased the muscle mass compared to the negative control. The increase was only in rats receiving (50 eugenol/20 mg/kg cerium oxide) was significant ($p<0.05$).

The sciatic nerve provides direct motor function to the leg muscles, anterior leg muscles and some leg muscles (9). It is important to determine whether sciatica is caused by an inflammatory disease or by direct compression of the nerve leading to more severe motor dysfunction. However, sciatica is often caused by inflammation. A wide range of pro-inflammatory factors including interleukin (IL)-β1, IL-6, IL-8 and tumor necrosis factor (TNF)-α have been observed in the serum of people with sciatica (10). Also, the damaged nerve is vulnerable to oxidative stress indicators. It has been observed that the increase of free radicals can contribute to the deterioration of the damaged nerve (11,12). Today, the use of nanotechnology in medicine has expanded. Nanomedicines as a new therapeutic approach have attracted the attention of researchers due to some special features such as greater effectiveness with lower doses and targeted delivery to tissues compared to chemical drugs. Cerium oxide nanoparticles have the capacity to actively remove all types of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in cell and animal models (13). Most of the therapeutic applications of cerium oxide nanoparticles are based on their ability to reduce the levels of inflammatory mediators such as inducible nitric oxide synthase (iNOS), nuclear factor kappa (NF-κB), tumor necrosis factor α (TNF-α) and interleukins (14). Recently, in a study, the neuroprotective effects of cerium oxide nanoparticles in improving peripheral nerves have been reported (15).

Eugenol (4-allyl-2-methoxyphenol) is a compound with anti-inflammatory and antioxidant activities (16). The findings show that the protective mechanism of eugenol may be partly attributed to reducing the production of pro-inflammatory cytokines through the regulation of inflammation (17). Also, previous studies have shown that eugenol inhibits the expression of iNOS through the regulation of NF-κB messenger pathways, including ERK1/2, I-κBα, p38 kinase (18).

Considering that peripheral nerve damage often occurs due to inflammation, therefore, inflammatory pathways can play an important role in causing sciatica. A previous study has also shown that pro-inflammatory factors and oxidative stress indicators increase in people with sciatica. Also, anti-inflammatory, antioxidant and neuroprotective effects of cerium oxide nanoparticles have been reported in several studies. In this study, eugenol was used as a natural compound. Eugenol has antioxidant, anti-inflammatory and neuroprotective properties. Also, previous studies have shown that eugenol exerts its effect by inhibiting the NF-KB pathway. Therefore, in this study, the mechanism of action of eugenol/cerium oxide is probably applied through the regulation of the inflammatory pathway and NF-κB. It is assumed that eugenol/cerium oxide by reducing inflammatory factors, iNOS and inhibiting the NF-KB pathway causes recovery of the sciatic nerve in rats.

Conclusion*:* The results of the findings showed that in rats receiving cerium oxide nanoparticles and eugenol, sciatic nerve recovery occurred faster. In fact, simultaneous injection of eugenol and cerium oxide nanoparticles synergistically increased sciatica function index and sciatic nerve improvement. Therefore, this drug combination may be considered as a target option for the repair of nerve tissue damage.

Keywords: **Cerium Oxide Nanoparticles, Eugenol, Sciatic**

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