Curcumin and Biodegradable Membrane Promote Nerve Regeneration and Functional Recovery After Sciatic Nerve Transection in Adult Rats

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Background: Curcumin has immunomodulatory anti-inflammatory, antioxidant, and neuroprotective properties. The goal of this study was to determine the effects of curcumin and biodegradable membrane on nerve healing in rat sciatic nerve transected injuries.

Methods: Rats were divided into groups: (1) control group (Ctrl), (2) curcumin group (Cur), (3) membrane group (Mem), and (4) membrane and curcumin group (Mem + Cur). Functional recovery was evaluated at 2, 4, 6, and 8 weeks after surgery. At the end of the eighth week after surgery, histological assessments were done.

Results: At the end of 8th week after surgery, functional assessments (sciatic nerve index, withdrawal reflex latency, and electromyography) in the Mem + Cur group improved compared with other groups ($P < 0.05$). Histological results (number of nerve fibers, diameter of nerve fibers, and myelin thickness) improved in the Mem + Cur group compared with the control, Cur, and Mem groups ($P < 0.05$).

Conclusion: The present study showed the positive effects of Mem + Cur on nerve regeneration of transected sciatic nerve in rat model.

Key Words: biodegradable membrane, curcumin, rat, repair, sciatic nerve

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Peripheral nerves are commonly exposed to physical injuries such as crushing, fractures, wounds, laceration, compression, and iatrogenic causes. Peripheral nerve injuries are a serious health concern for society, which always results in restricted activity, and many of trauma patients acquire lifelong disability.[1] Despite that microsurgical treatments for nerve injuries have been improved over the past decades, the best outcome remains unsatisfactory.

Following nerve injury, scar formation creates a mechanical barrier to the sprouting axons and might inhibit axonal regeneration. Thus, scar formation causes deformities and impairs normal function.[2] Several previous studies have investigated the effects of a range of scar-suppressing drugs. Nowadays, use of tissue-engineered nerves, which are typically composed of a physical scaffold, is an ideal option among various current alternatives. This scaffold mainly aids to create a favorable microenvironment for peripheral nerve regeneration. Recently, use of appropriate synthetic and natural materials has been studied as alternatives for peripheral nerve repair. As a result, much attention has been given by researchers and clinicians to chitosan. Chitosan is the N-deacetylated product of chitin and the second most abundant natural polysaccharide after cellulose, which is embedded in a protein matrix of a crustacean shell or a squid pen.[3,4] Chitosan has been studied for a number of useful properties such as biocompatibility, biodegradability, anti-inflammatory properties, wound healing, antitumor effects, and antibacterial properties. It is shown that chitosan avoids scar formation and provides space for the growth of regenerating axons.[5]

Commonly, microsurgical repair is required for the architectural reconstruction of the injured nerve, while neuroprotective drugs are used to promote nerve regeneration in the treatment of peripheral nerve injuries. Therefore, searching for effective drugs for promoting nerve regeneration, especially the naturally occurring ones, has gained extensive attention.

Curcumin (1,7-*bis*(4-hydroxy-3-methoxyphenyl)-1,6- heptadiene-3,5-dione) is a yellow polyphenol naturally occurring compound extract of medicinal *Curcuma* plants, especially found in the roots of *Curcuma longa* (Zingiberaceae). Curcumin possesses a variety of pharmacologic properties, including anti-inflammatory, antineoplastic, and antioxidant properties.[6] Its beneficial effects on various neurological diseases have also been shown.[7] In vitro studies showed the beneficial effects of curcumin on amyloid-induced toxicity in PC12 cells.[8] Recently, the neuroprotective capacities of curcumin have been increasingly recognized in both central and peripheral nervous systems.[9] In the peripheral nervous system, curcumin has been reported to accelerate motor functional recovery in a dose-dependent manner after sciatic nerve crush injury and raise the possibility that curcumin may promote nerve regeneration after peripheral nerve injuries.[10] In most recent studies, curcumin at 100 mg/kg has shown a protective effect on crush nerve injury, indicating the possibility of using curcumin as a neuroprotective agent in the treatment of nerve injuries.[5,6]

The aim of this study was to assess the potential protective effects of chitosan and curcumin on regeneration of transected sciatic nerve using hot-water paw immersion (for evaluation of sensory repair), Sciatic Functional Index (SFI; for evaluation of motor repair), and electromyographic (EMG; for evaluation of motor unit repair) and morphological assessments in a rat model of transected sciatic nerve.

MATERIALS AND METHODS

Animals

In the present experimental study, 28 male adult Wistar rats (180–200 g) purchased from Pasture Institute, Tehran, Iran (n = 7/group), were used in these experiments. The animals were kept in home cages at controlled temperature 23°C ± 2°C and 50% humidity with 12-/12-hour light-dark and have free access to standard rat chow and tab water. All experiments involving animals and surgical procedures were approved by the Ethical Committee of Baqiyatallah University of Medical Sciences.

Animal Grouping

In this experimental study, 28 rats were randomly divided into 4 groups (n = 7/group) as follows: (1) control group (Ctrl): transected and sutured sciatic nerve rats without any intervention; (2) curcumin group

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(Cur): curcumin 100 mg/kg per day (Sigma Co) was intraperitoneally administrated daily for 4 weeks after surgery; (3) membrane group (Mem): transected sciatic nerve rats were treated with membrane around the injured nerve; and (4) membrane + curcumin group (Mem + Cur): transected sciatic nerve rats were treated with membrane, and curcumin 100 mg/kg per day was intraperitoneally administrated daily for 4 weeks after surgery.

Membrane Preparation

Thin films were prepared with a mixture of 0.25 g of chitosan (low molecular weight with 85% deacetylation supplied by Sigma Co) and 0.08 g polyethylene oxide (molecular weight = 9×10^5 g/mol purchased from Sigma Co) dissolved in 50 mL of 1% acetic acid solution. The mixture was stirred for 2 hours at 40°C. The resultant solution was centrifuged at 2500 revolutions/min for 10 minutes to prevent air bubbles from forming. The mixture was cast into plastic Petri dishes with 75-mm diameter, dried at 25°C for 24 hours. The films were then dried and cut to patches of 1 × 1 cm.

Surgical Procedure

Animals were anesthetized with 80 mg/kg ketamine hydrochloride (Alfasan, the Netherlands) and 5 mg/kg xylazine hydrochloride (Alfasan) intraperitoneally. For sciatic nerve dissection, after the right hind limb was shaved, a longitudinal cutaneous incision was made in the posterolateral side of the thigh in length of 3 cm to expose the sciatic nerve. The right sciatic nerve was then transected at a midway by a sharp surgical knife. The epineurium was sutured with 7-0 Prolene sutures, and the muscle fascia and skin were then sutured with 4-0 nylon sutures.

SFI Assessment

Sciatic Functional Index was measured using an apparatus as follows. The SFI apparatus was made from wood with 60 × 7 × 20-cm (L, A, H, respectively) dimensions, and its floor was covered with white paper. Functional recovery was assessed at 2, 4, 6, and 8 weeks after surgery. Before the test, the rats' paws were painted with a water-soluble blue ink, then the rats were permitted to walk through the apparatus, and their footprints were tracked. The lengths of the third toe to its heel (PL), the second toe to the fourth toe (IT), and the first to the fifth toe (TS) were measured on the contralateral normal side (N) and the experimental side (E). Sciatic Functional Index was computed by the following modified formula:

SFI = −38.5 (EPL − NPL / NPL) + 109.5 (ETS − NTS / NTS) + 13.3 (EIT − NIT / NIT) − 8.8.

In this study, SFI oscillates around 0 for normal nerve function, whereas SFI around −100 represents total motor sciatic nerve dysfunction.[7]

Withdrawal Reflex Latency

Withdrawal Reflex Latency (WRL) test was performed using hot water bath (DID SABZ Co, Iran). The water temperature was set on 50°C ± 1°C. Measurement of reaction time in hot-water paw immersion test was done at 2, 4, 6, and 8 weeks after surgery. Paw immersion procedure was as follows: each rat was gently maintained by the experimenter, and one of its feet (ie, intact or experimental) immersed into the water until its paw. The time the rat withdraws its paw from the water was recorded and expressed as the reaction time. The procedure was repeated for 3 times with 10 minutes intervals and the average of reaction times was expressed as the resultant reaction time.[13]

At 8 weeks after surgery, the sciatic nerves were exposed in the anesthetized rats. The stainless steel electrodes were placed in the proximal site of the injured nerve, and electrical impulses (with duration of 0.1 millisecond and intensity of 2.3 mA) were applied. Amplitude and latency of the impulses were recorded as the factors of nerve conductivity from the gastrocnemius muscle, and a reference cap electrode was inserted on the knee joint. Another stainless steel needle was used as the ground electrode, which was inserted into the tail skin.[11]

Histological Analysis

For histological assessment, 8 weeks after surgery, the sciatic nerves were surgically taken out and fixed 10% formalin, embedded in paraffin. Five-micrometer transverse sections from distal portion of sciatic nerves were then stained by hematoxylin-eosin using standard techniques. The number of nerve fibers, diameter of nerve fibers, diameter of axons, and myelin thickness were assessed using MOTIC software (Nikon, Japan, 2001) under light microscopy from at least 5 randomly selected microscopic field in each rat at ×1000 magnification.

Statistical Analysis

All data are expressed as mean ± SEM. Results were analyzed using 1-way analysis of variance followed by least significant different post hoc test (SPSS 22.0 software package; SPSS Inc, Chicago, IL). Difference less than 0.05 ($P < 0.05$) level was considered as statistically significant.

RESULTS

SFI Evaluations

Immediately after surgery, the SFI values in all surgical groups significantly decreased to −100 compared with intact animals. During 2 and 4 weeks after surgery, there were no significant differences among groups ($P > 0.05$). At 6 weeks after surgery, SFI increased significantly in the Mem + Cur group compared with the Ctrl group ($P < 0.05$). At 8 weeks after surgery, SFI increased significantly in the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.01$, $P < 0.001$, and $P < 0.001$, respectively) (data shown in Table 1).

Withdrawal Reflex Latency

At 8 weeks after surgery, the reaction time in the WRL test decreased significantly in the therapeutic groups especially in the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.01$, $P < 0.001$, and $P < 0.001$, respectively). At 8 weeks after surgery, WRL decreased significantly in the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively) (data shown in Table 2).

TABLE 1. Use of Curcumin and Biodegradable Membrane Improved SFI After Sciatic Nerve Injury

Groups	Week 2	Week 4	Week 6	Week 8
Ctrl	86.56 ± 1.30	84.95 ± 2.89	81.59 ± 7.84	78.48 ± 0.88
Cur	86.29 ± 1.44	84.09 ± 2.54	81.07 ± 2.88	75.28 ± 5.23
Mem	85.87 ± 1.91	81.08 ± 1.49	75.67 ± 2.20	71.88 ± 3.32
Mem + Cur	84.95 ± 4.30	79.40 ± 3.36	74.28 ± 4.20*	64.90 ± 5.07†

Curcumin 100 mg/kg per day intraperitoneally administrated daily for 4 weeks after surgery significantly improved the SFI results in the right hindlimb in the Mem + Cur–treated group. Data are presented as mean + SEM.

*At 6 weeks after surgery, significant differences between the Mem + Cur group compared with the Ctrl group ($P < 0.05$).

†At 8 weeks after surgery, significant differences among the Mem + Cur group compared with the Mem, Ctrl, and Cur groups ($P < 0.05$ and $P < 0.001$, respectively).

TABLE 2. Use of Curcumin and Biodegradable Membrane Improved WRL after Sciatic Nerve Injury

Groups	Week 2	Week 4	Week 6	Week 8
Ctrl	7.80 ± 1.35	7.13 ± 0.52	6.81 ± 0.11	5.64 ± 1.90
Cur	7.59 ± 0.13	7.00 ± 0.39	6.04 ± 0.81	5.48 ± 1.29
Mem	7.43 ± 1.25	6.56 ± 0.94	4.77 ± 0.97	4.66 ± 0.58
Mem + Cur	7.28 ± 0.42	6.17 ± 1.40	4.47 ± 0.94*	3.07 ± 1.14†

Curcumin 100 mg/kg per day intraperitoneally administrated daily for 4 weeks after surgery significantly improved the WRL results in the right hindlimb in the Mem + Cur–treated group. Data are presented mean + SEM.

*At 6 weeks after surgery, significant differences among the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively).

†At 8 weeks after surgery, significant differences among the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.05$ and $P < 0.01$, respectively).

EMG Results

Our data showed that 8 weeks after surgery the latency in the Mem + Cur group was significantly decreased when compared with the Mem + Cur group compared with Cur, Ctrl and Mem groups ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively). In addition, at 8 weeks after surgery, mean amplitude (mV) was significantly increased in the Mem + Cur group compared with the Cur, Ctrl, and Mem groups ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively) (data shown in Table 3).

Histomorphometric Results

At 8 weeks after surgery, the numbers of nerve fibers increased significantly in the Mem + Cur group compared with other groups ($P < 0.001$). In addition, diameter of nerve fibers increased significantly in the Mem + Cur group compared with the Mem, Ctrl, and Cur groups ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively). About the diameter of the axons, there were no significant differences among the groups (Fig. 1). Furthermore, myelin thickness increased significantly in the Mem + Cur group compared with the Mem, Ctrl, and Cur groups ($P < 0.01$, $P < 0.001$, and $P < 0.001$, respectively) (data are shown in Table 4).

DISCUSSION

In the present study, the effects of chitosan/polyethylene oxide and curcumin were assessed on regeneration of transected sciatic nerve. It has been shown that behavioral analyses (SFI, withdrawal reflex latency, and EMG assessments) and histological changes, such as the number of myelinated nerve fibers, size of nerve, fiber and myelin thickness after sciatic nerve transection, improved at 8 weeks after surgery.

Our study was in agreement with Patzko et al,[12] who reported that use of oral 100 mg/kg curcumin has been shown to get rid of endoplasmic reticulum stress and reduce the activation of the unfolded protein response. As a consequence, clinical disability, electrophysiological parameters, and peripheral nerve morphology improved after use of 100 mg/kg curcumin. Also, our study was in agreement with Ma et al,[10] who reported that curcumin promoted nerve regeneration and functional recovery in a rat model of nerve crush injury so that use of higher doses of curcumin, for example, 100 mg/kg per day, showed better performance in improving nerve regeneration and functional recovery than low dose of curcumin. Our study was in disagreement with Agthong et al,[13] who reported that curcumin 200 mg/kg per day was given to a group of cisplatin-treated rats during 5 weeks, in the aspect of dose selected to investigate the effects of curcumin. The results showed that cisplatin induced thermal hypoalgesia on the fifth week, which could be prevented by curcumin. On the fifth and eighth weeks, sciatic motor nerve conduction velocity was reduced in the cisplatin compared with the control groups. Furthermore, curcumin also improved the reduced myelin thickness in the sciatic nerve of cisplatin-treated rats. Taken together, these findings suggested favorable effects on both functional and structural abnormalities in cisplatin neuropathy after use of curcumin.[13] Finally, our study was in agreement with Ma et al,[9] who reported that curcumin improved nerve regeneration and functional recovery, in the aspect of dose applied to investigate the effects of curcumin but not the same as the type of injury. In this regard, the curcumin groups at higher doses, for example, 100 mg/kg, showed higher SFI, shorter CMAP latency of onset, and higher amplitude of CMAP, highlighting its therapeutic values as a neuroprotective agent for peripheral nerve injury repair.

It is shown that curcumin at 100-mg/kg dose has protective effects on crush nerve injury. So, we selected curcumin at the previously mentioned dose. In addition, the period to investigate the effects of biodegradable membrane together with curcumin was 8 weeks after surgery because frequently functional recovery is reported to occur between 14 and 90 days after surgery. It should be mentioned that within hours of injury Wallerian degeneration begins, and by 6 to 8 weeks, this process is completed, leaving a distal stump comprising only endoneurial tubes lined by Schwann cells that is called bunger band. The Schwann cells are temporary; they will be disappearing if axonal regeneration does not occur. It is demonstrated that early nerve repair results in promoted functional outcomes. Previously, it is confirmed that myelinated nerve fibers had remarkably regenerated, scar formation was inconspicuous, and the myelin sheaths were dense and regular only 4 to 12 weeks after operation. Furthermore, it is reported that the regrowing axons have extended the gastrocnemius, the tibialis anterior, and the soleus muscles by 7 weeks. Thus, the EMG analyses were performed at 8 weeks after the surgery. In addition, many previous studies by this research group have been performed at 8 weeks after surgery that compared data together. Previously, the investigations were performed 4, 6, or 8 weeks after surgery.[14]

A variety of molecules are involved in the underlying pathogenesis of sciatic nerve injury, such as ischemia, free radical production, and apoptosis. Curcumin is an Indian spice and a natural compound. Curcumin exhibits various effects, such as anti-inflammatory and antioxidant properties. Various molecular targets are modulated by this agent, including cytokines and transcription factors.[15,16] It has been shown that after spinal cord hemisection curcumin inhibited apoptosis

TABLE 3. Use of Curcumin and Biodegradable Membrane Improved EMG Results After Sciatic Nerve Injury

Groups	Amplitude, mV	Latency, ms
Ctrl	3.57 ± 0.53	2.53 ± 0.27
Cur	4.14 ± 2.42	2.40 ± 0.38
Mem	5.34 ± 1.81	2.54 ± 0.53
Mem + Cur	5.34 ± 1.82*	1.82 ± 0.19†

Curcumin 100 mg/kg per day intraperitoneally administrated daily for 4 weeks after surgery significantly improved the EMG results in the right hindlimb in the Mem + Cur–treated group. Data are presented as mean + SD.

*Amplitude: at 8 weeks after surgery, significant differences among the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively).

†Latency: significant differences among the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.01$, $P < 0.05$, and $P < 0.01$, respectively).

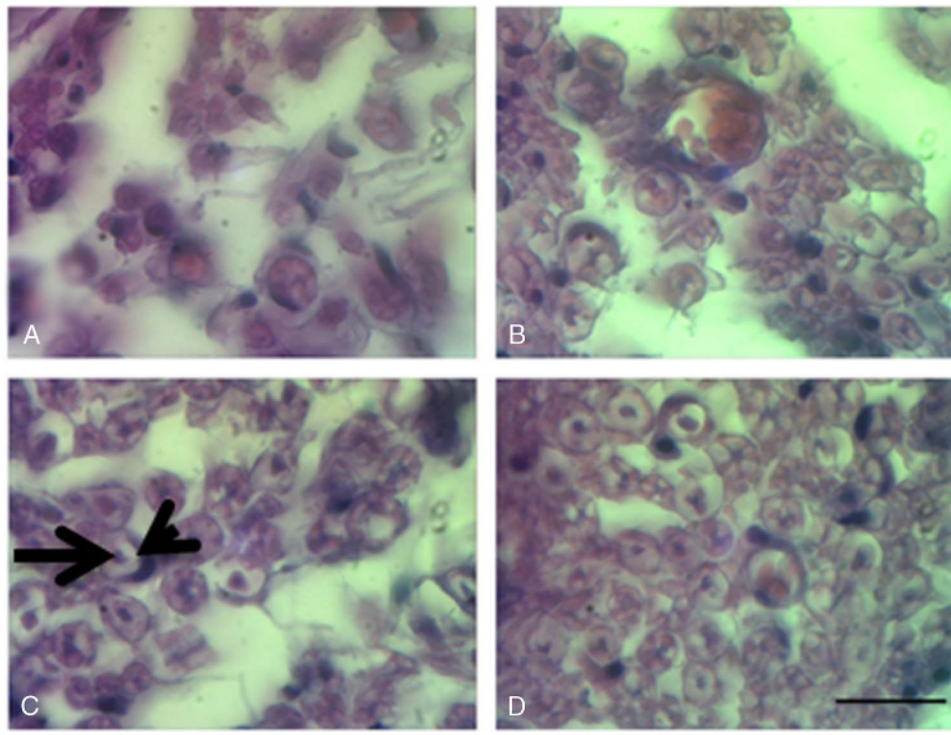

FIGURE 1. Photomicrographs of cross sections through distal part of damaged sciatic nerve at 8 weeks after surgery in different groups. A, Ctrl group, (B) Cur group, (C) Mem group, and (D) Mem + Cur group. Arrowhead: nerve fiber with Schwann cell, arrowhead: axon. Hematoxylin-eosin staining, original magnification ×1000.

and neuron loss.[15] In another survey, it has been demonstrated that treatment with *C. longa* extract attenuates the sciatic nerve injury and oxidative stress that follow. The authors reported that the antioxidative effect of *C. longa* extract, even when delayed for 24 hours, may have a potential role as a protective agent in the neurodegenerative process.[17] These findings are in accordance with the present study, in which we evaluated the protective effects of curcumin on nerve injury.

In addition, chitosan has been reported to have various anti-inflammatory properties. Antioxidants are well known for their beneficial effects on health. They protect the body against reactive oxygen species, which exert oxidative damage to membrane lipids, protein, and DNA. In recent years, much effort has been invested to investigate the antioxidant activity of chitosan and its derivatives. It is reported that chitosan and its derivatives have oxygen radical–scavenging activity. Low-molecular-weight chitosans are more active in scavenging free radicals.[18] It is demonstrated that use of chitosan on the site of nerve transection has beneficial influence on the development of posttraumatic neuroma and reduction of extraneural fibrosis.[19] In fact, chitosan avoids scar formation and provides a suitable microenvironment for axon regeneration.

TABLE 4. Use of Curcumin and Biodegradable Membrane Improved Histological Analyses After Sciatic Nerve Injury

Groups	No. Nerve Fibers	Diameter of Nerve Fiber, μm	Diameter of Axons, μm	Myelin Thickness, μm
Ctrl	38.08 ± 3.38*	3.34 ± 0.74	1.20 ± 0.17	1.67 ± 0.60
Cur	46.08 ± 6.94	3.36 ± 1.13	1.3 ± 0.48	2.21± 0.32
Mem	47.08 ± 1.78	3.59 ± 0.72	1.56 ± 0.14	2.98 ± 0.49
Mem + Cur	46.66 ± 7.42†	3.79 ± 1.03‡	1.46 ± 0.44	2.19 ± 0.69§

Curcumin 100 mg/kg per day intraperitoneally administrated daily for 4 weeks after surgery significantly improved the histological results in the right hindlimbs in the Mem + Cur–treated groups. Data are presented mean + SEM.

*About number of nerve fibers: at 8 weeks after surgery, significant differences among the Ctrl group compared with the Cur, Mem, and Mem + Cur groups ($P < 0.01$, $P < 0.01$, and $P < 0.001$, respectively).

†About number of nerve fibers: at 8 weeks after surgery, significant differences among Mem + Cur compared with Cur, Mem, and Ctrl groups ($P < 0.01$, $P < 0.01$, and $P < 0.001$, respectively).

‡About diameter of nerve fibers: significant differences among Mem + Cur compared with Cur, Mem, and Ctrl groups ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively). Diameter of axons: there were no significant differences among groups.

§About myelin thickness, significant differences among the Mem + Cur group compared with the Mem, Cur, and Ctrl groups ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively).

It is reported that chitosan enhances the production of transforming growth factor β1, platelet-derived growth factor, and interleukin 1 by stimulating macrophages.[5] In injured peripheral nerves, the entry of macrophages and their activation lead to phagocytosis of debris, followed by their clearance from the nerve. These well-coordinated sequences of macrophage responses prepare the distal segment to receive regenerating axon sprouts. The macrophage response terminates by down-regulation of proinflammatory cytokines and the up-regulation of anti-inflammatory ones.

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