Anti-neuropathic effect of different extracts of Rosmarinus officinalis leaves in the rat

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Rosmarinus officinalis L. (Laminaceae), commonly called rosemary, grows spontaneously in Europe, Asia and Africa. Leaves of *R. officinalis* possess a variety of bioactive properties including antioxidant, antitumor, antinflammatory and antinociceptive. Its main constituents are a group of phenols, mainly rosmarinic acid, several flavonoids and a class of diterpenoids. Among them, carnosic acid (CA) is recognized as one of the most potent antioxidant constituent and recent evidence highlighted its ability to modulate the cholinergic system inhibiting the AChE activity.

Aimed to individuate a new therapeutic strategy to relieve neuropathic pain, three different extracts ethanol (EE), acetone (AE) and ultrasound-hexane (URE) from rosemary leaves were tested in a rat model of peripheral neuropathy induced by the loose ligation of the sciatic nerve (Chronic Constriction Injury; CCI). The extracts were characterized in terms of content of typical constituents: EE contained rosmarinic acid (4,1%) and carnosic acid (1,9%); AE was characterized by an high amount of carnosol (12,6%) and by the absence of carnosic acid and rosmarinic acid; URE was further enriched in carnosic acid (up to 13,43%) with a low content of carnosol (1,5%). The extracts were orally administered once a day for 13 days starting from the day of the surgery. On day 14, AE (100 and 300 mg kg^{-1}) was more potent and efficacious than EE in relieving mechanical hyperalgesia (Paw pressure test) and allodynia (Von Frey test) and spontaneous pain (Incapacitance test).

Repeated administrations of the URE extract (69 mg kg^{-1}) fully reverted CCI-induced neuropathic pain evaluated as mechanical and thermal hypersensitivity (Plantar test) as well as hind limb weight bearing alterations. These effects paralleled with those induced by a comparable dose of pure carnosic acid (13.4 mg kg^{-1}per os once a day for 13 days) strongly suggesting the relevance of this compound in the anti-neuropathic effect of rosemary. Moreover, URE was able to significantly prevent morphological alterations of the sciatic nerve induced by CCI and evaluated as number of fibers, axon diameter and myelin thickness. Finally, a pharmacodynamic mechanism was proposed since the co-administration of the nicotinic blocker mecamylamine (2.0 mg kg^{-1}intraperitoneally twice daily for 13 days) significantly antagonized the URE effects on pain relief and neuroprotection.

In conclusion, the extract of rosemary leaves is active against neuropathic pain and prevents nervous tissue alterations by a mechanism involving the nicotinic cholinergic system. The main role of carnosic acid is highlighted.