Astragalus membranaceus Extracts: a Preclinical Study for the Treatment of Chemoterapy-Induced Neuropathy

L. Di Cesare Mannelli[1], M. Zanardelli[1], L. Micheli[1], D. Baptista De Souza[1], L. Cinci[1], A. Karioti[2], E. Gallo[1], A. Pacini[3], F. Firenzuoli[1], A.Vannacci[1], A.R. Bilia[2], A. Mugelli[1], C. Ghelardini[1]

[1]Dept. of Neuroscience, Psychology, Drug Research and Child Health - Neurofarba - Pharmacology and Toxicology Section, University of Florence, Italy
[2]Dept. of Chemistry, University of Florence, Italy
[3]Dept. of Experimental and Clinical Medicine - Anatomy and Histology Section, University of Florence, Italy

Neurotoxicity is the limiting side effect of the anticancer agent oxaliplatin. A tangled panel of symptoms, sensory loss, paresthesia, dysesthesia, pain, are characteristic of oxaliplatin-induced neuropathy, and may be disabling for patients adversely affecting quality of life. Pharmacological treatments demonstrating a therapeutic effect on oxaliplatin's cumulative neurotoxicity are unsatisfactory and limited to symptomatic effects. New, fully active, compounds leading to mechanism based therapies that prevent/treat the neuropathic pain face and improve neurorestoration need.
In a rat model of painful oxaliplatin-induced neuropathy (2.4 $mgkg^{-1}$ intraperitoneally, daily for 21 days), we previously described a pattern of molecular and morphological alterations of both peripheral and central nervous system. Among biochemical signs, oxidative stress has been evidenced as an important component. In this model common antioxidant compounds shows a significant even if incomplete antihyperalgesic activity, with a good correspondence with the clinical evidences.
Astragalus membranaceus is an adaptogenic herb from the traditional Chinese medicine and the root of this herb has been described as preventative in free radical-induced damage. Aimed to study the antineuropathic profile of this plant, aqueous, alcoholic and hydroalcoholic extracts from selected roots of *A. membranaceus* were obtained. In a primary rat astrocyte cell culture, the aqueous extract reduced by 55% the superoxide anion ($O_2^{-\cdot}$) production evoked by oxaliplatin; the hydroalcoholic extract reduced $O_2^{-\cdot}$ by 35% and the alcoholic one by 15%. The hydroalcoholic extract was the most active in preventing the oxaliplatin-dependent apoptotic process.
In vivo, *A. membranaceus* was tested in the described model of chemotherapy-induced neuropathy. All the extracts were 300 $mgkg^{-1}$ per os administered once a day, starting from the first day of oxaliplatin injection until the 20^{th}. On the day 21^{st} *A. membranaceus* extract treatments were able to significantly reduce oxaliplatin-dependent pain, when evaluated as an increase on suprathreshold stimulation (hyperalgesia-related measure; Paw pressure test) or as a decrease in pain threshold (allodynia-related measure; Von Frey and Cold plate tests). In particular, the hydroalcoholic extract fully prevented mechanical hyperalgesia and cold allodynia suggesting a pharmacodynamic that outclasses the antioxidant mechanism. The higher efficacy of this kind of product along with the antiapoptotic properties prompted us to evaluate its protective effects *ex vivo*. *A. membranaceus* hydroalcoholic extract strongly prevented the serious nephro- and hepato-toxicity induced by repeated treatment with the anticancer drug. In the nervous system the hydroalcoholic extract reduced the morphometric alterations induced by oxaliplatin in the dorsal root ganglia, and significantly prevented the changes in the activating transcription factor 3 and in the phosphorylated heavy chain of neurofilament expression levels both in nerves and ganglia. Finally, the protective effect of *A. membranaceus* did not interfere with the oxaliplatin antineoplastic in vitro mechanism as evaluated on a human colon adenocarcinoma cell line (HT29).
The hydroalcoholic extract of *Astragalus membranaceus* relieves pain and promotes the rescue mechanisms that protect nervous tissue from the damages triggering chronic pain. A safe profile strongly suggests the usefulness of this natural product in oxaliplatin-induced neuropathy.