DIOSMETIN RELIEVES PAINFUL SYMPTOMS CAUSED BY ANTINEOPLASTICS IN PRECLINICAL MODELS OF ACUTE AND CHRONIC PAIN

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INTRODUCTION: Cancer patients experience painful symptoms as an antineoplastic therapy adverse effect. Paclitaxel, a chemotherapeutic drug, causes peripheral neuropathic pain, characterised by mechanical and thermal hypersensitivity. Aromatase inhibitors, like anastrozole, used as adjuvant therapy for hormone-positive breast cancer in postmenopausal women, are also associated with painful symptoms. Clinically duloxetine is used for the relief of chemotherapy-induced peripheral neuropathy, and seems beneficial in reducing the aromatase inhibitors' painful symptoms. Despite this, duloxetine's benefits remain limited, searching for new therapies is necessary. Diosmetin is a flavonoid found in natural plant products and is also chemically synthesized, preclinical studies demonstrated systemic diosmetin's efficacy in treating neuropathic pain. **OBJECTIVE:** Investigate the effects of diosmetin in models of paclitaxel-induced neuropathic pain and anastrozole-induced musculoskeletal pain in mice. **MATERIALS AND METHODS:**To assess mechanical and cold allodynia, and nociceptive-induced affective-motivational behavior, male C57BL/6 mice (CEUA #4400060223) were used. We analyzed a dose-response curve of diosmetin (0.015, 0.15 and 1.5 mg/kg, oral) in mice submitted to paclitaxel-induced acute (1 mg/kg, intraperitoneal) and chronic (4 x 1 mg/kg, intraperitoneal) pain syndromes. Duloxetine (30 mg/kg, oral) was used as a reference drug. We also assessed the effect of diosmetin in the anastrozole (0.2 mg/kg, oral) induced musculoskeletal pain model alone or associated with paclitaxel. **RESULTS:** Diosmetin educed paclitaxel-induced acute and chronic pain syndrome, and duloxetine reduced mechanical allodynia, but did not affect nociceptive-induced affective-motivational behavior symptoms, cold allodynia or heat hyperalgesia, Diosmetin also alleviated anastrozole-induced nociception in mice and reduced nociception evoked by the association of paclitaxel plus anastrozole. **CONCLUSION:** Diosmetin reduced the nociceptive symptoms caused by paclitaxel and by association paclitaxel plus anastrozole. In this sense, diosmetin presents a potential alternative to treatments currently used to relieve pain induced by antineoplastic drugs.

Keywords: Nociception, Anticancer treatment, Flavonoid.

References: Molecular Neurobiology (accepted for publication); Bray et al., 2024 (10.3322/CAAC.21834); Bennett et al., 2019 (10.1097/J.PAIN.0000000000001363); Glare et al., 2014 (10.1200/JCO.2013.52.4629); Loprinzi et al., 2020 (10.1200/JCO.20.01399); Gupta et al., 2020 (10.1200/OP.20.00113); Marquezin et al., 2024 (10.1007/s10787-024-01473-4).

Acknowledgments: FAPERGS (21/2551–0001966-2), CAPES, CAPES/PROEX (1333/2023; 88887.568915/2020-00; 88887.875443/2023-00), CNPq (309404/2023-1; 152071/2024-5). FAPERGS/PROBIC.