

CHEMICAL PROFILES AND PHARMACOLOGICAL ACTIVITY OF TWO ANTHEMIS SPECIES: ANTHEMIS TINCTORIA VAR. PALLIDA AND A. CRETICA SUBSP. TENUILOBA

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Introduction: Members of Anthemis genus are extensively used in the Turkish folk medicine to treat various ailments. In this present study, the ethyl acetate, methanolic and aqueous extracts of aerial the parts of Anthemis tinctoria var. pallida (ATP) and A. cretica subsp. tenuiloba (ACT) growing in Turkey were investigated for their phytochemical profile, antioxidant and neuroprotective effects.

Materials and methods: The extracts' chemical profiles were evaluated using UHPLC-ESI/HRMS, while colorimetric methods were used to evaluate their antiradical effects and enzyme inhibition activity on cholinestrases, α -amylase, α -glucosidase, and tyrosinase. Finally, we studied Anthemis extracts in an experimental model of cortical spreading depression (CSD), in order to explore potential neuroprotective effects.

Results: Results collected in the present study indicated the promising biological effects of ATP and ACT extracts. Tested extracts showed very good antioxidant activity and potent inhibitory effects against key enzymes involved in Alzheimer's disease, type II diabetes, and hyperpigmentation conditions. The pharmacological study also highlighted the capability of ATC water extract to blunt CSD-induced increase in lactate dehydrogenase (LDH) level and serotonin (5-HT) turnover. Additionally, this extract revealed able to restore physiological activity of specific proteins involved in neuron morphology and neurotransmission, including neurofilament (NFEM) proteins, protein C kinase γ (PKC γ) and vesicle-associated membrane protein-2 (VAMP-2).

Discussion and conclusions: CSD is a pathophysiological and mass depolarization of neurons and glial cells which is characterized by a change in ion and water distribution across neuron membrane associated with cytotoxic effects, including neuron death. Excitotoxicity depolarizing-stimuli ($K^+ \geq 50$ mM) were reported to increase significantly 5-HT overflow, which could stimulate neurotransmitter turnover, thus explaining the cortical 5-HT depletion induced by CSD, *in vivo*. CSD has been also described as a potential triggering mechanism in migraine with aura, via the activation of trigeminal nociceptive system, both peripherally and centrally. While low 5-HT state could play a pivotal role in migraine attack, through multiple effects, including the reduction of the threshold of pain perception, the increased tendency of having headache and the interference with the control of cerebrovascular nociception. An untargeted proteomic profile was also performed on rat cortex homogenate, in order to investigate the putative mechanism of action. Collectively, the neuroprotective effects exerted by ATC water extract, in CSD models, suggest potential applications in the management of clinical symptoms related to neuroinflammatory conditions, including migraine.