CHEMICAL PROFILING AND PHARMACO-TOXICOLOGICAL ACTIVITY OF ORIGANUM SIPYLEUM EXTRACTS: EXPLORING FOR NOVEL SOURCES FOR POTENTIAL THERAPEUTIC AGENTS

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Introduction: The genus Origanum (belonging to the Lamiaceae family) comprises 56accepted species which consist of a group of herbaceous perennials with culinary and medicinal uses. Many species are present in the Mediterranean region, especially Turkey, which has a rich oregano diversity and trade. Origanum sipyleum L. is a 80 cm tall perennial semi-shrub, with pink flowers and more than one stiff stem. The plant usually prefers warm climates and grows well in arid soils rich in nutrient, mostly calcareous, similar to other Origanum taxa. This species has been used as medicinal tea, food additive, and for essential oil production. In central Anatolia, O. sipyleum is extensively used as a spice, and in west Anatolia it is used for treating gastrointestinal disorders and cough. Preliminary phytochemical analysis of aqueous and methanol extracts of the aerial parts showed the presence of terpenoids, flavonoids, tannins, and anthracenes. Fingerprint analysis of methanolic extract of the flower also revealed a wide plethora of phenolic compounds, the main ones being apigenin, caffeic acid, carvacrol, hesperidin, naringenin, rosmarinic acid, rutin, and vitexin. With regards to its biological properties, multiple extracts of O. sipyleum were found to display scavenging effect against DPPH and hydroxyl radicals, and were also able to reduce the formation of peroxides in the thiocyanite method, and molybdenum (VI) to molybdenum (V) in the phosphomolybdenum method. Moreover, the methanolic extract of the flower was effective against 13tested bacteria except against Yersinia enterocolitica. The most sensitive bacteria were Mycobacterium smegmatis, Psendomonas aeruginosa, and Salmonella enteritidis.

Materials and methods: In this study, the antiradical and enzyme inhibition activity of three solvent extracts (ethyl acetate, methanol, and aqueous) of O. sipyleum was assessed. The chemical fingerprint profile of the extracts was assessed using spectrophotometric and LC-MS techniques. Furthermore, we performed a pharmacological study in order to explore the antioxidant and anti-inflammatory effects induced by the extracts in an experimental model of ulcerative colitis.

Results: LC-MS analysis revealed that the extracts contained different classes of phenolics. DPPH, ABTS, CUPRAC and FRAP tests showed that aqueous extract was the most active as antiradical agent. The same extract also showed the strongest activity as acetylcholinesterase (AChE) inhibitor. These results are consistent with total phenol (171.74mg GAE/g extract) and flavonoid content (39.68mg RE/g extract) that were higher in the aqueous and ethyl acetate extract, respectively. We also found that all extracts were effective in reducing colon levels of pro-oxidant and pro-inflammatory biomarkers, including nitrites, lactate dehydrogenase, prostaglandin $E_2$and serotonin, in an experimental model of ulcerative colitis, with the best activity showed by ethyl acetate extract. Similarly, O. sipyleum extracts have been subsequently assayed on bacterial and fungal species involved in ulcerative colitis, finding a significant inhibition on C. albicans and S. aureus. Finally, we evaluated the antiproliferative effects exerted by the extracts on human colon cancer HCT116cell line, finding that only ethyl acetate extract was able to reduce cell viability, despite being ineffective on spontaneous cell migration.

Discussion and conclusion: Concluding, phytochemical analysis indicated that the three solvent extracts varied in their composition, antioxidant and enzyme inhibition profile. Additionally, our findings of reduced pro-oxidant/pro-inflammatory biomarkers induced by the extracts, together with the inhibitory effects on selected bacterial and fungi strains involved in ulcerative colitis and the antiproliferative effect on HCT116cells, further support potential applications of O. sipyleum extracts in the management of clinical symptoms related to ulcerative colitis.