INHIBITION OF HUMAN cAMP PHOSPHODIESTERASES AS A MECHANISM OF THE SPASMOLYTIC EFFECT OF *MATRICARIA RECUTITA L.* WATER EXTRACT

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Tea infusions of *Matricaria recutita* L. flowers is a herbal remedy used for the treatment of gastro-intestinal (GI) complaints, including minor spasms, epigastric distensions, and belching (1). The spasmolytic activity has been shown *in vitro* and in clinical studies (1). cAMP and cGMP levels regulate the GI smooth muscle tone causing relaxation. Inhibition of phosphodiesterase (PDEs), which catalyze the hydrolysis of cAMP and cGMP to 5'AMP and 5'GMP (2), is one of the mechanisms operated by spasmolytic drugs. In this study the effect of water extracts of dried capitula and sifted flowers on the activity of cAMP- and cGMP-PDEs was investigated. For this purpose, human recombinant PDE5A1 was prepared by expression of the full-length cDNA of PDE5A1 into COS-7 cells (3); cAMP-PDE activity was evaluated in human platelet homogenate. PDE activity was determined according to (4). Tea infusions (1g dried flowers/60 ml water at boiling temperature) were prepared from both capitula and sifted chamomile, and lyophilized. The recovery was 28.5 ± 2.2 and 26.5 ± 0.8 % on the dried drug, respectively (mean ± SD, n=6). Infusions were tested at concentrations of 5-100 µg/ml. The extracts showed only a negligible effect on PDE5A1 while inhibited cAMP-PDE in a concentration-dependent fashion; the IC_{50} values ranged from 18.0 to 27.2 µg/ml for water extracts from capitula flowers (WECF), and from 20.5 to 40.5 µg/ml for water extracts from sifted flowers (WESF). WECF and WESF showed a similar inhibitory effect on cAMP-PDE. To investigate which component/s could be responsible for the effect, apigenin-7-glucoside (AP-7-glu), luteolin-7-glucoside (LU-7-glu), the corresponding aglycons apigenin (AP), luteolin (LU), α-bisabolol, herniarin, umbelliferone, and chamazulene were tested. At 10 µM, only flavones derivatives inhibited cAMP-PDE, while the other compounds were inactive. The IC_{50} values followed this order: LU>AP>AP-7-glu≥LU-7-glu, ranging between 1.3 and 14.9 µM. All flavonoids at 50 µM inhibited PDE5A1 activity, at a lower extent than cAMP-PDE. Quantitative determination of AP-7-glu and LU-7-glu by LC-MS/MS showed that WECF contained more AP-7-glu than LU-7-glu, whereas the opposite was observed for WESF. In conclusion, the spasmolytic action of chamomile may be mediated by cAMP-PDE inhibition, although other mechanisms can not be excluded.

(1) ESCOP monography; (2) Beavo J.A. (1995) Physiol. Rev. 75, 725-748; (3) Dell'Agli M., Galli G., Vrhovsek U., Mattivi F., Bosisio E. (2005) J. Agric. Food Chem. 53, 1960-1965; (4) Kincaid R.L., Manganello V.C. (1988) Methods Enzymol. 159, 45-470.