2nd Symposium on Medicinal Chemistry of University of Minho

8 May 2015

SCHOOL OF SCIENCE, CHEMISTRY DEPARTMENT

Campus de Gualtar

Inhibition of the VEGFR-2 tyrosine kinase domain by wild Roman chamomile extracts and phenolic compounds

Rafaela Guimarães,[a,b] Ricardo C. Calhelha,[a,b] Hugo J.C. Froufe,[b] Rui M.V. Abreu,[b] Ana Maria Carvalho,[b] Isabel C.F.R. Ferreira,[b] Maria João R.P. Queiroz,[a]

[a]*Centro de Química da Universidade do Minho, Escola de Ciências, Campus de Gualtar 4710-057 Braga, Portugal; mjrpq@quimica.uminho.pt*
[b]*Centro de Investigação de Montanha, Escola Superior Agrária, Instituto Politécnico de Bragança, Campus de Santa Apolónia, apartado 1172, 5301-854 Bragança, Portugal*

Angiogenesis results from new blood vessels growing excessively (e.g. cancer). The Vascular Endothelial Growth Factor (VEGF) is secreted by the tumor cells and plays a crucial role in angiogenesis; low oxygen tension dramatically induces the expression of this major angiogenic factor that when linked to the transmembrane tyrosine kinase receptor VEGFR-2, which is present in endothelial cells, signalizes for the proliferation of these cells towards the tumor. Treatments using small molecules with anti-tyrosine kinase activity (e.g., sorafenib) can block angiogenic signalling, reduce blood tumoral irrigation, and improve chemotherapy distribution [1]. Some studies recognized phenolic compounds as chemopreventive agents, especially flavonoids. Other plant-derived anticancer drugs (e.g. Taxol) proved to be anti-angiogenic. In traditional Chinese medicine, many herbs are used in the treatment of angiogenic diseases such as chronic wounds and rheumatoid arthritis [2]. Furthermore, it has been reported that drinking of green tea could inhibit VEGF-induced angiogenesis *in vivo* [3]. In the present work, the anti-angiogenic activity of Roman chamomile (*Chamaemelum nobile* L.) extracts (methanolic extract and infusion) and main phenolic compounds (apigenin, apigenin-7-*O*-glucoside, caffeic acid, chlorogenic acid, luteolin, luteolin-7-*O*-glucoside) was evaluated through an enzymatic assay using the VEGFR-2 tyrosine kinase domain. To better understand the inhibition phosphorylation mechanism of the tyrosine kinase receptor by luteolin, apigenin and apigenin-7-O-glucoside, docking studies were performed. The methanolic extract showed higher phosphorylation inhibition than the infusion (IC_{50} values of 269 and 301 µg/mL, respectively). Regarding phenolic compounds, luteolin (IC_{50} 2.10 µM) and apigenin (IC_{50} 4.78 µM) were the most potent in inhibiting VEGFR-2 phosphorylation, leading us to believe that these compounds are involved in the anti-angiogenic activity revealed by the methanolic extract.

Acknowledgments:
The authors acknowledge FCT (Portugal) POPH-QREN and FSE for the research grants of R. Guimarães and R. Calhelha (SFRH/BD/78307/2011 and SFRH/BPD/68344/2010, respectively).

References:
[1] Morère, J.F., Brechot, J.M., & Etessami, R., *Targeted Oncology*, **2006**, *1*, 215-219.
[2] Fan, T.-P *et al., Trends in Pharmacological Sciences*, **2006** 27, 297-309.
[3] Maiti, T.K., Chatterjee, J., & Dasgupta, S., *Biochemical and Biophysical Research Communications*, **2003**, 308, 64-67.