ARTICLE IN PRESS

International Immunopharmacology xxx (2011) xxx-xxx

Contents lists available at ScienceDirect



International Immunopharmacology



journal homepage: www.elsevier.com/locate/intimp

Letter to the Editor

Propolis as anti-inflammatory and anti-allergic compounds: Which role for flavonoids?

Dear Dr. Talmadge,

A recent article by Nakamura R. and colleagues has reported the effects of propolis from different geographical areas on mast cell degranulation [1]. As well as flavonoids, propolis is well known among general population for its anti-allergic properties [2,3]. Actually, propolis has plenty of biological and pharmacological properties and its mechanisms of action have been widely investigated in the last years, using different experimental models in vitro and in vivo. While several researchers are interested in the investigation of isolated compounds responsible for propolis action, there is lack of clinical research on the effects of this substance; so, clinical investigation is needed to evaluate propolis potential in patients or healthy individuals, in order to understand under which conditions propolis may promote health and prevent allergy or inflammatory ailments. Some criticism about propolis benefits has also been raised [4,5], anyway propolis appears to represent nowadays one possible investment for research in drug therapy of allergy [3]. Biological activity of propolis may depend on the geographical area from which the propolis is produced, as this should affect the composition in polyphenolic compounds with healthy and/or preventive potential. In Chinese propolis the following flavonoids were identified in ethanol extracts by normal-phase chromatography: chrysin, galandin, kaempferol, 3-O-methyl-kaempferol but however their amounts in the fractions were very low [1]. While water (WEP) and ethanol (EEP) extracts from propolis coming from Brazil had a higher content in flavonoids than propolis from China, the latter proved to possess the strongest inhibition of antigen-induced mast cell degranulation and the lowest harmful effects on RBL-2H3 mast cell lines [1]. This evidence should suggest that anti-allergic and/or anti-inflammatory activity of propolis, rather than on single molecules, might depend on a complex interaction between different natural phenolic compounds. Phenolic acids, such as caffeic acid, and flavonoids belong to the same polyphenolic derivatives from phenylalanine and shikimic acid biochemical pathway: their kinship gives them the potential to behave as competitors or as synergistic substances, depending on doses, composition in extracts, cell type and molecular asset.

Chrysin and kaempferol were identified as the major anti-allergic components in EEP. Chrysin is commonly present in propolis [2]; it was associated, as a main dietary component with quercetin, to the UV-induced suppression of the contact hypersensitivity (CHS) response to picryl chloride (PCl) in SKH-1 mice [6], and, as with apigenin, to the down-regulation of IgE high affinity receptor (FccRI) in basophil line KU812, due to ERK1/2 kinase inhibition [7]. Kaempferol effects on basophil and mast cells have been extensively reviewed [2] and one suggestion for its inhibitory effect exerted on RBL-2H3 comes from the involvement of heme oxygenase-1 [1]. The presence of caffeic acid phenetyl ester (CAPE) in Chinese propolis as a current inhibitor of mast cell degranulation, is another hallmark of phenolic compounds as antiallergic substances. Caffeic acid is commonly present in propolis

1567-5769/\$ – see front matter \circledast 2011 Elsevier B.V. All rights reserved. doi:10.1016/j.intimp.2011.03.018

together with flavonoids [8]. CAPE is able to suppress the induction of eotaxin in human lung fibroblast cells [9] and eotaxin is a potent chemoattractant for eosinophils, basophils and T-helper type 2 lymphocytes but, anyway, this mechanism cannot be suited to a purified mast cell line in the absence of other cell types. This compound is able to inhibit directly some kinases involved in the allergic response, such as Fyn kinase [10]. The inhibition of Fyn kinase can affect degranulation but a role for the intact functional protein has been suggested, as it leads to IgE-mediated FccRI down-regulation by suppressing receptor beta-chain mRNA [11]: this example should suggest that a phenolyc compound may have theoretical different effects even if it targets the same protein. However, more insights about the intracellular suppression mechanism of mast-cell response to IgE-mediated activation led by these compounds need to be highlighted and claim that further investigations have to be addressed. Whether a synergistic mechanism between CAPE and some flavonoid, such as chrysin in reaching the inhibitory degranulating response of RBL-2H3 mast cell line to antigen-mediated stimulation does occur, we are currently unable to know; however, such hypothesis, may open the way to discuss about the role of other or "accessory" components in a plant extracts as well known anti-allergic substances, besides flavonoids. This perspective should promote the use of nature-derived herbal formulas compared to purified molecules, but many complex issues and contradictory opinions have yet to be faced, the main of which is related to the role of single components as either inhibitorscompetitors or promoting agents depending on the molecular milieu of polyphenolic mixtures and/or cell environment and targets.

So, which roles for flavonoids in allergy and inflammation?

The huge amount of plant polyphenolic compounds, of which flavonoids occupy about half (4000 different molecules), do not make easy to find a straightforward answer: questions remain about the real cellular function targeted by these compounds either alone or within a plant extract mixture. Nevertheless, the best perspective is to focus onto the many subtle cellular mechanisms by which signals are read and interpreted within the complex network of intracellular components, such as kinases, phosphatases, receptors and transcription factors. The screening of the enormous array of plant secondary metabolites, first of all polyphenols, for new effective and safe antiinflammatory agents should be rather directed towards molecules targeting specific inflammatory pathways [12,13]. Many particular dose-related phenomena, such as hormesis, should be considered in this context in order to achieve a better comprehension of several biphasic and paradoxical effects (pro- or anti-) of phenolic plant products as promising tools for human health [14,15].

Disclosure

The author declares that he has no conflict of interest.

References

 Nakamura R, Nakamura R, Watanabe K, Oka K, Ohta S, Mishima S, et al. Effects of propolis from different areas on mast cell degranulation and identification of the effective components in propolis. Int Immunopharmacol 2010;10(9):1107–12.

Please cite this article as: Chirumbolo S, Propolis as anti-inflammatory and anti-allergic compounds: Which role for flavonoids? Int Immunopharmacol (2011), doi:10.1016/j.intimp.2011.03.018

2

Letter to the Editor

- [2] Chirumbolo S. The role of quercetin, flavonols and flavones in modulating inflammatory cell function. Inflamm Allergy Drug Targets Sep 2010;9(4):263–85.
- Sforcin JM, Bankova V. Propolis: is there a potential for the development of new drugs? J Ethnopharmacol Oct. 21 2010, doi:10.1016/j.jep.2010.10.032. [3]
- [4] Propolis: hypersensitivity reactions. Prescrime Int Aug. 2010;19(108):170.
 [5] Münstedt K, Kalder M. Contact allergy to propolis in beekeepers. Allergol Immunopathol (Madr) 2009;37(6):298-301.
- Steerenberg PA, Garssen J, Dortant P, Hollman PC, Alink GM, Dekker M, et al. [6] Protection of UV-induced suppression of skin contact hypersensitivity: a common feature of flavonoids after oral administration? Photochem Photobiol 1998;67(4): 456 - 61
- Yano S, Tachibana H, Yamada K. Flavones suppress the expression of the high-[7] affinity IgE receptor FcepsilonRI in human basophilic KU812 cells. J Agric Food Chem Mar 9 2005;53(5):1812-7.
- [8] Gregoris E, Stevanato R. Correlations between polyphenolic composition and antioxidant activity of Venetian propolis. Food Chem Toxicol 2010;48(1):76-82.
- Liao YR, Hsu JY, Chu JJ, Fu LS. Caffeic acid phenethyl ester suppresses the induction [9] of eotaxin in human lung fibroblast cells. J Asthma 2010;47(3):233-7.
- [10] Kang NJ, Lee KW, Shin BJ, Jung SK, Hwang MK, Bode AM, et al. Caffeic acid, a phenolic phytochemical in coffee, directly inhibits Fyn kinase activity and UVBinduced COX-2 expression. Carcinogenesis 2009;30(2):321-30.
- [11] Brenzovich J, Macey M, Fernando J, Chong HJ, Barnstein B, Mirmonsef P, et al. IgE signaling suppresses FcepsilonRlbeta expression. J Leukoc Biol 2009;86(6): 1351-8

- [12] Kostyuk V, Potapovich A, De Luca C. The promise of plant polyphenols as the golden standard skin anti-inflammatory agents. Curr Drug Metab 2010;11(5): 414-24
- [13] Chirumbolo S, Marzotto M, Conforti A, Vella A, Ortolani R, Bellavite P. Bimodal action of the flavonoid quercetin on basophil function: an investigation of the putative biochemical targets. Clin Mol Allergy 2010:8:13–24.
- Vargas AJ, Burd R. Hormesis and synergy: pathways and mechanisms of quercetin [14] in cancer prevention and management. Nutr Rev Jul 2010;68(7):418–28.
- [15] Kay CD. The future of flavonoid research. Br J Nutr 2010;104:S91–5.

Salvatore Chirumbolo

Department of Pathology and Diagnostics, Section General Pathology, University of Verona, Italy, Strada Le Grazie 8 37134 Verona, Italy Tel.: + 39 0458027553: fax: + 39 0458027127. *E-mail address:* salvatore.chirumbolo@univr.it.

> 13 January 2011 Available online xxxx