

Anti-inflammatory property of propolis

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(Received 5 September, 2014; Accepted 8 December, 2014; Published online 7 February, 2015)

Dear Editor-in-Chief,

The recent article by Weina Gao and colleagues, on July issue of this Journal, showed that Brazilian green propolis has a positive effect on innate and adaptive immunity in aged mice.⁽¹⁾ This role should be mainly attributed to flavonoids contained in propolis.⁽²⁾ The Authors reported that Brazilian propolis had 189.12 mg/g total polyphenols, 98.46 mg/g flavonoids, 1.95 mg/g cinnamic acid and 23 mg/g artemillin-C.⁽¹⁾ Yet, the participation of any single molecule to the reported evidence in aged animals might have involved different spectra of activity and different molecular targets in promoting the beneficial action observed by the Authors.⁽¹⁾ Artemillin C, namely (E)-3-[4-hydroxy-3,5-bis(3-methylbut-2-enyl)phenyl]prop-2-enoic acid, is one of the major component in Brazilian propolis and recent reports have stressed its ability to block the serine/threonine protein kinase known as PAK-1.⁽³⁾ PAK proteins are critical effectors that link the Rho family of GTPases to the cytoskeleton reorganization and nuclear signaling; These proteins serve as targets for the small GTP binding proteins Cdc42 and Rac and have been implicated in a wide range of biological activities, for example PAK1 regulates cell motility and morphology, furthermore the role of Cdc42 GTPases activating protein in aging has been recently reported.⁽⁴⁾

The involvement of PAK1 in inflammatory and neurodegenerative disorders suggests that this molecules is targeted in aging mechanism. Few natural PAK1-blockers such as rosmarinic acid, curcumin and caffeic acid extend the lifespan of the nematode *Caenorhabditis elegans* or fruit flies.⁽⁵⁾ PAK1 promotes reproduction, whereas it inactivates HSP16.2 gene and shortens lifespan, as do also PI-3 kinase (AGE-1), mTOR, and insulin-like signalling (ILS) (Daf-2) in this nematode.⁽⁵⁾ It is arguable that caffeic acid and particularly artemillin-C play a role in slowing aging cellular mechanism and synergistically exert an anti-inflammatory action with propolis flavonoids.⁽⁴⁾ This suggestive

speculation may appear contradictory when data from serum in aged mice, showing a marked increase in inflammatory cytokines on increasing Brazilian propolis assumption, are considered.⁽¹⁾ The Authors concluded that this evidence assessed the improvement in inflammatory response caused by propolis in aged mice.⁽¹⁾ This circumstance addresses the positive role exhibited by nature-derived phytochemicals on stressed, dysregulated, aged or infected (inflamed) cells. Therefore, while a wide literature exists reporting the anti-inflammatory role of flavonoids,⁽⁶⁾ many data from clinics should suggest a pro-inflammatory role exerted by polyphenols in restoring health, prevent cancer onset and degenerative disorders.⁽⁷⁾ Fundamentally, as like as in propolis, the most proper idea about the activity of nature-derived polyphenols and phenolic substances, should deal with the concept of immune modulation, depending on the cell nature and homeostatic balance, not merely an improvement given by inhibition or promotion coming from the molecular nature of these molecules. Propolis is widely used as an anti-inflammatory raw substance, especially during allergy and airway inflammatory disorders. The interesting paper by Weina Gao *et al.*, would suggest that in elderly people Brazilian propolis may ensure a health promoting action by activating the immune response.⁽¹⁾ This is formally true but literature reports many data with potentially misleading evidence about. A combination therapy (anti-inflammatory drugs plus propolis) in aged adults showed encouraging results⁽⁸⁾ and, moreover, due to yet contradictory results from clinics,⁽⁹⁾ respect to *in vitro* and animal evidence,^(1,10) a more cautious, critical and less enthusiastic debate about this substance has to be taken into account in the next future.

Looking forward to a kind reply from yours.

Conflict of Interest

No potential conflicts of interest were disclosed.

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Author's response re: "Anti-inflammatory property of propolis"

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(Received 24 November, 2014; Accepted 8 December, 2014)

Dear Editor-in-Chief

We appreciate the interesting and helpful comments made by Dr. Salvatore Chirumbolo⁽¹⁾ on our article entitled "Brazilian green propolis improves immune function in aged mice".⁽²⁾ Our study investigated the effects of Brazilian green propolis on immunological parameters, such as cytokines, peritoneal macrophages function and antibodies in aged mice. The results demonstrated that administration of Brazilian green propolis had a positive effect on immune function in aged mice.

IL-1 β , IFN- γ and IL-4 are cytokines secreted by macrophage, Th1 and Th2 cells, respectively and vital in maintaining normal immune function. For example, IL-1 β is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis. IL-4 is known to be active in the stimulation of B and T cell proliferation and the differentiation of B cells into plasma cells. IFN- γ is critical in the protection against viral, some bacterial and protozoal infections.⁽³⁻⁵⁾ It has been demonstrated that aging is often accompanied with decreased production of IL-1 β , IL-4 or IFN- γ and compromised immune function.⁽⁶⁻⁸⁾ Therefore, it should be beneficial when the production of these cytokines is recovered to some extent in the aged. In our study, serum IL-1 β , IL-4 and

IFN- γ showed an increasing trend after Brazilian green propolis treatment in aged mice and meanwhile, some immunological parameters were also improved. A number of studies conducted in several different laboratories also indicated that propolis, as well as some of its components, was active in increasing the secretion of several cytokines and the mechanisms involved are not clear yet.⁽⁹⁻¹⁴⁾ It should be pointed out that overproduction of some cytokines is not beneficial and frequently associated with inflammatory response or autoimmunity, as raised kindly by Dr. Salvatore Chirumbolo.⁽¹⁾ However, no statistic significance was found for serum contents of IL-1 β , IL-4 and IFN- γ among different groups in our study, suggesting that IL-1 β , IL-4 and IFN- γ were not overproduced at the doses we administrated. It is not certain whether the production of IL-1 β , IL-4 and IFN- γ will be enhanced further if more propolis is administrated.

We consider that Brazilian green propolis is potential to be a regulator of immune/inflammatory response or an immunoenhancer and may have a health promoting action in the aged, though further studies in elderly subjects are needed. It is also necessary to further investigate the roles played by individual compounds present in Brazilian green propolis, such as artemillin C, cinnamic acid or other components.

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