MICROBIOLOGY FOR SURGICAL INFECTIONS

DIAGNOSIS, PROGNOSIS AND TREATMENT

Edited by

Kateryna Kon MD, PhD
Kharkiv National Medical University, Kharkiv, Ukraine

Mahendra Rai MSc, PhD
Sant Gadge Baba Amravati University, Amravati, Maharashtra, India
Department of Chemical Biology, Institute of Chemistry, University of Campinas, Campinas SP, Brazil

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-411629-0

Printed and bound in United States of America

14 15 16 17 18 10 9 8 7 6 5 4 3 2 1

CHAPTER

13

The Role of Honey and Propolis in the Treatment of Infected Wounds

Ananias Pascoal[*], *Xesus Feás*[†], *Teresa Dias*[*], *Luís G. Dias*[*] *and Leticia M. Estevinho*[*]

***CIMO-Mountain Research Center, Department of Biology and Biotechnology, Agricultural College of Bragança, Polytechnic Institute of Bragança, Bragança, Portugal, †Department of Organic Chemistry, Faculty of Sciences, University of Santiago de Compostela, Lugo, Spain**

INTRODUCTION

Honey

Honey is defined as the natural substance produced by *Apis mellifera* bees from plant nectar, from secretions of the living parts of plants, or from the excretions of plant sucking insects feeding on the living parts of plants.[1,2] Honeybees collect, transform, and combine this with specific substances of their own, and then store it and leave it in the honeycomb to ripen and mature. This natural product is generally composed of a complex mixture of carbohydrates and other less common substances, such as organic acids, amino acids, proteins, minerals, vitamins, lipids, aroma compounds, flavonoids, pigments, waxes, pollen grains, several enzymes and other phytochemicals.[3–5] However, the specific composition depends on many factors, such as the nectar composition of the source plant, the species of bee, the climate, environmental and seasonal conditions, agricultural practices and treatment of honey during extraction and storage.[6–9]

As a natural, unprocessed and easily digested food, honey plays an important role in the human diet, and is also used in pharmaceutical and cosmetic industries.[10]

Modern science has studied the medical significance of honeys in healing wounds and burns,[11] oncology care,[12] as well as its antioxidant and antimicrobial properties.[3,13,14]

Microbiology for Surgical Infections
DOI: http://dx.doi.org/10.1016/B978-0-12-411629-0.00013-1

Propolis

Propolis (bee glue) is a beehive product prepared by bees of the *Apis mellifera* species, using resinous substances collected from various plants.[15,16] These substances are mixed with the β-glycosidase enzyme of their saliva, partially digested, and added to bee wax to form the final product.

This product, commonly referred as a "natural antibiotic", has an important role in protecting, reinforcing and repairing the hives. In addition, any invaders are wrapped in propolis and die by asphyxia, then the bodies are preserved, which prevents the putrefaction of the honeycomb.[17–19] It is also a barrier to molds and yeasts, bacteria, viruses, and rain. Propolis is mainly composed of resins (50%), waxes (30%), essential oils (10%), pollen (5%), and other organic compounds (5%), among which are phenolic compounds, esters, flavonoids, terpenes, aromatic aldeydes and alcohols.[20–23] However, it is worth mentioning that this composition differs significantly with botanical and geographical origin and depends on climatic conditions, terrain, water availability and other environmental factors.[18,24–28]

It has been reported that this product has several pharmacological properties, such as antibiotic, anti-neoplastic, anti-inflammatory,[26] anti-diarrheatic, antimicrobial,[29,30] antiviral,[31] antioxidant,[32] hepatoprotective, cardiostatic,[33] antitumoral,[23,34] anti-ulcerus and immunostimulatory activity.[35,36] Other studies highlight its efficiency as an anti-HIV-1,[37] anti-neurodegenerative[38] and anti-tuberculosis agent.[39]

Due to these medicinal properties, propolis is generating increasing interest from the pharmaceutical, food and cosmetic industries, and it is currently being introduced in products for human consumption, such as drinks and food additives.[32,40]

PHENOLIC AND FLAVONOID COMPOUNDS

Honey

Phenolic compounds are one of the most important groups of plant secondary metabolites, comprising at least 8000 different known structures. Their chemical structures range from simple phenolic molecules to high molecular weight polymers of approximately 30000 Da.[41] These compounds are reported to exhibit anticarcinogenic, anti-inflammatory, anti-atherogenic, anti-thrombotic, immune modulating, analgesic, antineoplatic behavior, antiviral activity, antiulcer properties, hormone, antibiotic and cardiovascular activities, among others, and exert these functions as antioxidant activities.[42,43] In addition, flavonoids inhibit lipid peroxidation, platelet aggregation, capillary permeability and the activity of enzyme systems including cyclo-oxygenase and lipoxygenase.[10,44] The honey phenolics and the flavonoids present in honey are divided into three classes with similar structure; flavonols, flavones and flavanones. These are important due to their contribution to honey color, taste and flavor and also due to their beneficial effects on health. In honey, propolis and royal jelly, most of the phenolic compounds are present in the form of flavonoids, whose concentration depends on various factors, including the plant species used by the bees, the health of the plant, and seasonal and environmental factors.[6,7,45,46] So, the properties of

honey are expected to vary with the composition of the active compounds it contains.[47] According to references 48 and 49, the principal flavonoids present in honey, propolis and royal jelly are flavonoles (quercetin, kaempherol, galangin, fisetin), flavanones (pinocembrin, naringin, hesperidin), and flavones (apigenin, acacetin, chrysin, luteolin).

According to one study, *p*-hydroxibenzoic acid, cinnamic acid, naringenin, pinocembrin and chrysin were the phenolic compounds present in most of the Portuguese honey samples analyzed by high-performance liquid chromatography with a diode array detector.[10] Since then many other studies have been performed to look at the total phenolics and flavonoids of honey from different regions and countries.[50–54] Luteolin, quercitrin and isorhamnetin were the flavonoids detected in Meliponinae honey (MH) from the Ecuadorian stingless bee.[55] Other studies analyzed local, unprocessed, multifloral honey[56] and observed that the main flavonoids were luteolin, quercetin, apigenin, kaempferol, isorhamnetin, acacetin, tamarixetin, chrysin, and galangin. In general, the results of a range of studies provide clear information about the the similarities of phenolic compounds found in honey samples. However, even though the results obtained by references 10, 50, 51, and 54 partly agree with other papers, there is great qualitative and quantitative variability in the flavonoid content of bee honeys from different geographical areas. It can be stated that more lipophilic flavonoids (pinocembrin, chrysin, genkwanin and tectochrysin) are found in propolis and beeswax; therefore they are regarded as not being related to the floral origin of honey.[57] The rest of the flavonoids are considered to originate from the nectar or the pollen and are therefore directly related to the botanical origin of the honey, which is entirely dependent on the nectar foraged by the bees.[58]

Propolis

The total quantity of polyphenols and flavonoids in propolis are important parameters for evaluating its quality and biological potential.[32] The specific phenolic composition of propolis is extremely dependent on the plants found around the hive, as well on the geographic and climatic characteristics of the location.[20] Existing studies on the chemical composition of European propolis have only determined and identified the phenolic compounds and flavonoids.[18,26] These compounds have been extracted using different solvents: water, methanol and ethanol. Higher concentrations of flavonoids were obtained in hydro-alcoholic extracts than in methanol or water solvents.[26] These results agree with the data presented in reference 32, which considers propolis from the northeast of Portugal. However, reference 59 obtained inferior values when analyzing propolis from the south of the same country. This discrepancy may be due to the great distances between the locations of origin, and differences in apicultural practices. In fact, the results obtained by reference 26 suggest that propolis from different places contains different concentrations of polyphenols.

It is generally accepted that propolis from temperate climatic zones, like Europe, North America and the non-tropical regions of Asia, originate mainly from the bud exudates of *Populus* species and their hybrids, and are rich in flavonoids, phenolic acids and their esters,[20,60] while propolis from tropical regions, where no poplars and birches exist, are rich in prenylated benzophenons, diterpenes and flavonoids.[61–63]

Other studies revealed that the caffeic acid phenethyl ester (CAPE) is a biologically active ingredient of propolis with several interesting biological properties, including enhancing apoptosis,[64] reducing metastasis,[65] and increasing radiation sensitivity[66] of cancer cells. Additionally, the propolis from tropical zones, in particular the southeastern region of Brazil, were shown to be rich in prenylated phenylpropanoids,[20] although non-typical flavonoids from "poplar type" propolis, such as kaempferide and isosakuranetin, have also been found.[67,68] Moreover, Cuban propolis has recently caught the attention of scientists because its peculiar enrichment in polyisoprenylated benzophenones makes it chemically distinct from both European and Brazilian bee glue.[69]

Recently, new compounds have been isolated from propolis, such as 3,5-diprenyl-4-hydroxycinnamic acid (artepillin C) from Brazilian green propolis, which may be a key immunomodulatory compound.[70] It was reported that CAPE and artepillin C are the two most immunopotent chemicals found in propolis.[71] Artepillin C, which is a low-molecular-weight phenolic compound, is uniquely found in Brazilian green propolis and is one of its main constituents.

ANTIMICROBIAL ACTIVITY IN THE TREATMENT OF INFECTED WOUNDS AND IN WOUNDS HEALING

Honey

It has been reported that the bacteria in wounds increases oxygen consumption and thus reduces the level of oxygen available to the wound tissues to a point where tissue growth is impaired.[72] The consequences of bacterial infection are non-healing wounds, an increase in wound size, the development of ulcers and abscesses, failure of skin grafts, inflammation, swelling, and pain.[73] Studies have revealed that more than 80 bacteria and yeasts are efficiently inhibited by honey.[74,75] Emerging evidence from clinical studies suggests that honey is at least as effective as conventional treatments for healing wounds, particularly in very refractory cases such as in diabetics, the elderly, and extensively burned patients.[76,77] Antibiotic resistance is a public health problem with severe consequences, such as the increasingly difficult treatment of chronic wounds. In this context, it is essential to find alternative treatments; hence bee products and their derivatives may be very useful in this area. Indeed, many studies have assessed the effectiveness of honey for healing wounds that are not responsive to conventional antibiotics and antiseptics.[78–81]

Several studies revealed that honey has a broad spectrum antibacterial activity at the concentrations used in dressings, with unreported microbial resistance in laboratory wounds.[82] In the last decade, the antimicrobial activity of honey (new, stored, heated, heated and stored and exposed to ultraviolet light) was tested at concentrations in aqueous dressing medium varying between 10 and 100% (w/v) for its activity against common human pathogens.[83,84] This biological activity was tested in acidic, neutral, and alkaline media. In one study,[83] surgical wounds were made on the dorsa of mice and infected with *Staphylococcus aureus* or *Klebsiella* sp. and then treated with local application of honey four times a day. Appropriate antibiotics were also used and compared with the control values. The application of honey four times a day was compared with the effect of conventional antibiotics in rats with bacterial conjunctivitis induced by *Escherichia coli*, *Proteus* sp.,

S. aureus, Klebsiella sp. *Haemophilus influenza* , and *Pseudomonas aeruginosa*. It was verified that the growth of all the isolates was completely inhibited by 30−100% honey concentrations, with *E. coli, P. aeruginosa*, and *H. influenza* being the most sensitive. The effects of storage on the biological activities of the product were investigated, and the study showed that heating at 80°C for 1 hour followed by 5 years storage decreased the antimicrobial activity of honey, but other conservation methods, such as exposure to ultraviolet light, increased its activity against some microorganisms.[83]

Studies have assessed the *in vitro* antimicrobial activity of different concentrations of honey ether extracts against *Candida albicans*, the most prevalent fungal pathogen in humans, using agar-well diffusion and broth micro-dilution methods.[56] Even though honey flavonoids inhibited the growth of the yeasts, they did not kill them, and did not directly affect their cytoplasmic membrane.

Honey has also been reported to be useful in the healing of infected postoperative wounds,[85] where its effectiveness combines with other useful characteristics; it is non-irritating, non-toxic, self-sterile, bactericidal, nutritive, and easily applied.[86] Therefore, honey has advantages as a wound dressing because it provides a moist healing environment and prevents bacterial growth even when the wounds are heavily infected. It is an effective means of rendering heavily infected wounds sterile quickly and of inhibiting the growth of antibiotic resistant strains of bacteria. Its viscosity acts as a further barrier against wound infection.[87]

In a clinical study involving 59 patients with wounds and ulcers,[88] most of which had failed to respond to conventional treatments, fresh honey was applied daily. The bacteria isolated from these wounds (*E. coli, S. aureus, Proteus mirabilis*, mixed coliforms, *Klebsiella* sp., and *Enterococcus faecalis*) were all susceptible to honey *in vitro*. Another clinical study comprising 50 patients with wounds compared the use of honey as a treatment with the antiseptic Savlon (15% cetrimide, 1.5% chlorohexidine gluconate).[89] Honey cleared 60% of the treated wounds in 6 days whereas Savlon cleared only 36% of wounds within the same period. Another study used honey on nine infants with large infected surgical wounds that had failed to heal with intravenous antibiotics, cleaning the wound with aqueous 0.05% chlorhexidine solution and applying fusidic acid ointment.[90] Marked clinical improvement was seen in all cases after five days of treatment with honey, and all wounds were closed, clean and free of infection after 21 days of this application. Other studies report that two randomized controlled clinical trials have compared honey with silver sulfadiazine ointment on partial-thickness burns. Both showed that honey gave better control of infection.[91] It was observed that honey allowed successful skin grafting in wounds infected with *Pseudomonas* which had not responded to other treatments.[79] Other authors report the efficiency of the use of honey in patients suffering from wound breakdown after operation for carcinoma of the vulva.[92]

It was observed that manuka honey promoted the healing in venous leg ulcers, giving effective de-sloughing and a lower incidence of infection than the control.[93] In a further study of the use of honey as a wound dressing, honey was evaluated in the treatment of wounds of various etiologies, including diabetic ulcers, and the results indicated that it promoted granulation and epithelization of the wounds, reduced odor and had a dehydrating effect.[87] There are reports of a reduction in edema and pain[94] and improvements in healing outcomes[93] being observed clinically in various types of wound.

A recently published study[82] assessed a series of geographically and chemically-defined New Zealand manuka, kanuka and manuka-kanuka blended honeys containing varying concentrations of methylglyoxal (MGO) and hydrogen peroxide to determine their effectiveness in inhibiting the growth of different species of bacteria (*Bacillus subtilis, S. aureus, E. coli and P. aeruginosa*). The author observed that the three manuka honey samples analyzed had the highest MGO contents, and were the most effective in inhibiting the growth of *B. subtilis, E. coli* and *S. aureus,* with all the observed levels of growth inhibition being similar. Low honey concentrations (1−4%) caused significant lag-phase extension and bacterial growth was completely inhibited once concentrations reached 8−16%. Therefore the author demonstrated the potency of natural honey as an antimicrobial wound dressing, and that a range of effects arise from the variety of active compounds present, which not only allow active honey to have a broad spectrum of activity, apparently free of undesirable side effects, but also reduce the potential for resistant microbial populations to evolve.

Propolis

The research reported in reference 95 indicates that propolis delays growth and progression of skin changes in the early stage of infection with Herpes simplex and does not cause cytotoxicity. It was reported that propolis extracts can be used locally in viral infections.[31] The study in reference 96 verified the synergism between ciprofloxacin and propolis in the treatment of experimental *S. aureus* keratitis. It was also suggested that the simultaneous use of propolis and antibiotics may reduce the acquisition of resistance, and consequently remove the need for more powerful antibiotics.[97] Propolis may also show synergistic effects with antimicrobial drugs, and its association with commercially disposable drugs is a field of interest in the development of new products by the pharmaceutical industry.[98] It was reported that propolis diminished the resistance of the bacterial wall to antibiotics (amoxicillin, ampicillin and cefalexin)[99] and acted synergistically with antibiotics acting on ribosomes (chloramphenicol, tetracycline and neomycin).[100] Another study showed that propolis included in an ointment base influences the healing process and stimulates the proliferation of keratinocytes, in a way that depends on the wound healing stage.[101] A study of propolis ointment demonstrated its superior wound healing effect in comparison with the classical treatment of silver sulfadiazine.[102] The possibility of treating burn lesions with propolis was reported in clinical studies.[103] In a previous study of the use of propolis to treat cutaneous erythema, it was found to induce severe collagenization, but the use of propolis in open wounds results in normal collagenization. This leads to the conclusion that propolis acts differently upon the collagenization process depending on the lesion type.[104]

OTHER APPLICATIONS OF HONEY AND PROPOLIS IN HUMAN HEALTH

Honey

Honey has been used as a traditional medicine for centuries, by different cultures and for the treatment of a range of disorders. Reference 105 opines that honey with a high level

of antibacterial activity has the potential to reduce the risk of dental caries. In addition to the carioprotective effect of New Zealand manuka honey, Molan and co-workers have shown from his extensive work on the influence of honey on oral health that honey prevents dental plaque, gingivitis, and periodontics.[106] Other workers in different laboratories have also shown that honey is non-cariogenic or less cariogenic than sucrose, which may be due to the protective role of its constituents, among which are inorganic ions and other colloidal components.

The case of a patient with persistent fistulas, resistant to conventional therapy, that were completely healed after six months of treatment with honey has also been reported.[107] Recent studies[108] compared the clinical and mycological cure rates of a novel mixture consisting of honey and yogurt with local antifungal agents for treating patients with vulvo-vaginal candidiasis during pregnancy, and obtained very promising results.

Several authors have reported the antibacterial activity of honey against bacteria causing life-threatening infections in humans. The effectiveness of honey in killing *Proteus* spp, *S. aureus*, *E. coli* and *P. aeruginosa* bacterial strains involved in urinary tract infections, diarrhea, septicemia, diabetic foot ulcers, community acquired nosocomial infections and wound infections has been widely reported.[109–111] Other studies also highlight the activities of honey in killing *Mycobacterium* tuberculosis.[112] Another study tested a monofloral honey, and found that it successfully eradicated the bacterial flora in the conjunctival sac after seven days of continuous administration. The study involved patients in the perioperative period of cataract surgery or vitrectomy.[113] The results obtained indicate that honeydew honey may act as a prophylactic agent of endophthalmitis. Another study[114] tested the *in vitro* antiviral effect of manuka and clover honeys at concentrations ranging from 0–6% (w/v) against a clinical varicella zoster virus. Their results showed that both types of honey showed antiviral activity *in vitro* against this virus with an approximate EC50 = 4.5 % (w/v). Other studies reported the use of honey in treating diarrhea,[115] and found that it may effect repair of the intestinal mucosa damaged by the infection;[116] it was used to treat peptic ulcers and gastritis infected by *Helicobacter pylori*,[117] to treat Fournier's gangrene, and found to promote rapid healing,[118] especially in first and second degree burns.[119]

Propolis

The research carried out in reference 120 indicated the effectiveness of a propolis extract in reducing the growth of bacteria that belong to the red complex (*Fusobacterium nucleatum*, *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus* and *Tannerella forsythia*). The studies in references 121–123 confirmed the antibacterial properties of propolis in relation to pathogens of periodontitis. According to some authors,[121] the antibacterial effects are due to flavonoids, phenol acids, and their esters. The results in reference 124 showed the clinical effectiveness of a toothpaste and gel containing a 3% ethanolic extract of propolis in a group of patients with a greater risk of gingivitis caused by dental plaque. As propolis rinses the mouth, and propolis-based toothpastes stop the growth of pathogens of gingivitis and periodontitis, these materials

seem to be promising not only as preventive but also as therapeutic agents.[122,125] The results obtained by reference 126 showed, however, that propolis extracts in concentrations that effectively reduce pathogenic organisms for periodontal diseases are cytotoxic for the gingival fibroblasts.

The first report of the biological activity of Portuguese propolis demonstrated that propolis displays effective antiproliferative activity against human renal cancer cells. Furthermore, a comparison of the *in vitro* responses of normal and malignant cells to propolis extracts revealed that cancerous cells were more sensitive in terms of growth inhibition than normal cells. The study[127] reported the main constituents of an aqueous extract of Brazilian green propolis from Southeast Brazil and the effects of the orally administered aqueous extract on distinct phases of wound healing (cellular recruitment and extracellular matrix deposition) in a murine sponge model. Their results showed a decrease in cellular recruitment after treatment with propolis. It has been reported that phenolic compounds exert a wide range of biological actions, such as antioxidant activity by scavenging free radicals.[101] Propolis has been found to exert indirect cytotoxic effects on malignant cancer cell lines by activating macrophages.[128] Its anti-inflammatory role and wound healing promoting properties have also been reported: studies[129–131] have examined the *in vitro* effect of a Chilean propolis ethanolic extract on human spermatozoa treated with benzo[a]pyrene and exogenous reactive oxygen species. The work demonstrates that the natural drug under investigation is able to protect genomic DNA from damage induced by benzo[a]pyrene, hydrogen peroxide and hydrogen peroxide in combination with adenosine 5V-diphosphate (ADP) and ferrous sulfate ($FeSO_4$), producing a significant reduction in intracellular oxidants. A propolis extract was shown to possess the capacity to protect sperm membranes from oxidative attack, suggesting that it may have a role in protection against male infertility.

CONCLUSIONS AND FUTURE PROSPECTS

According to the literature referred to in this chapter, beehive products are useful, not only in the treatment of infected wounds, but also in other medical conditions.

Even though some studies provide enough information and trials to hypothesize the introduction of beehive products on the clinical practice, it must be ensured that the quality parameters are met, for example, that they are free of microbiological contaminations and pesticides. Indeed, the general applicability of honey requires its safe preparation and is hampered by the insufficient knowledge of its composition and mechanisms of action, as well as lack of standardization. One possibility would be to apply the beehive products topically, initially as a complement to conventional therapy. In addition, the lack of reported resistance supports the use of honey and propolis as a new approach for treating multidrug resistant wounds.

Taking into account the current limitations, future studies must thoroughly characterize the biological activities of these products, by analyzing the underlying mechanisms of action and isolating the most beneficial compounds, mainly those related to preventing microorganisms developing drug resistance.

References

1. Codex Alimentarius. Revised Codex Standard for Honey, Codex STAN 12–1981, Rev. 1 (1987), Rev. 2. (2001).
2. EU. Council directive 2001/110/CE relating to honey. *Off J Eur Communities* 2002;**L10:**47–52.
3. Gomes S, Dias L, Moreira L, Rodrigues P, Estevinho L. Physicochemical, microbiological and antimicrobial properties of commercial honeys from Portugal. *Food Chem Toxicol* 2010;**48**:544–8.
4. Lazarevic JS, Palic RM, Radulovic NS, Ristic NR, Stojanovic GS. Chemical composition and screening of the antimicrobial and antioxidative activity of extracts of *Stachys* species. *J Serb Chem Soc* 2010;**75**:1347–59.
5. Erejuwa OO, Sulaiman SA, Wahab MSA. Honey: A novel antioxidant. *Molecules* 2012;**17**:4400–23.
6. Al-Mamary M, Al-Meeri A, Al-Habori M. Antioxidant activities and total phenolic of different types of honey. *Nutr Res* 2002;**22**:1041–7.
7. Yao L, Datta N, Tomás-Barberán FA, Ferreres F, Martos I, Singanusong R. Flavonoids, phenolic acids and abscisic acid in Australian and New Zealand *Leptospermum* honeys. *Food Chem* 2003;**81**:159–68.
8. Marchini LC, Reis VDA, Moreti ACCC. Composição fisico-química de amostras de pólen coletado por abelhas africanizadas *Apis mellifera* (Hymenoptera: Apidae) em Piracicaba, Estado de São Paulo. *Ciência Rural* 2006;**36**:949–53.
9. Iglesias A, Feás X, Rodrigues S, Seijas JA, Vázquez-Tato MP, Dias LG, et al. Comprehensive study of honey with protected denomination of origin and contribution to the enhancement of legal specifications. *Molecules* 2012;**17**:8561–77.
10. Estevinho L, Pereira AP, Moreira L, Dias LG, Pereira E. Antioxidant and antimicrobial effects of phenolic compounds extracts of northeast Portugal honey. *Food Chem Toxicol* 2008;**46**:3774–9.
11. Molan PC. Potential of honey in the treatment of wounds and burns. *Am J Clin Dermatol* 2001;**2**:13–9.
12. Bardy J, Slevin NJ, Mais KL, Molassiotis A. A systematic review of honey uses and its potential value within oncology care. *J Clin Nurs* 2008;**17**:2604–23.
13. Theunissen F, Grobler S, Gedalia I. The antifungal action of three South African honeys on *Candida albicans*. *Apidologie* 2001;**32**:371–9.
14. Akbulut M, Ozcan MM, Coklar H. Evaluation of antioxidant activity, phenolic, mineral contents and some physicochemical properties of several pine honeys collected from Western Anatolia. *Int J Food Sci Nutr* 2009;**60**:577–89.
15. Souza BM, Palma MS. Peptides from *Hymenoptera* venoms. In: Lima MH, Pimenta AMC, Martin-Eauclaire MF, Zingali R, Rochat H, eds. *Animal toxins: state of the art – perspectives in health and biotechnology*. Editora UFMG; 2009. pp. 345–67.
16. Santos VR. Propolis: alternative medicine for the treatment of oral microbial diseases. In: Sakagamai H, ed. *Alternative medicine*; 2012. pp. 133–69.
17. Salatino A, Teixeira E, Negri G, Message D. Origin and chemical variation of Brazilian propolis. *Evid Based Complement Alternat Med* 2005;**2**:33–8.
18. Falcão SI, Vilas-Boas M, Estevinho LM, Barros C, Domingues MR, Cardoso S. Phenolic characterization of Northeast Portuguese propolis: usual and unusual compounds. *Analyt Bioanalyt Chem* 2010;**396**:887–97.
19. Umthong S, Phuwapraisirisan P, Puthong S, Chanchao C. *In vitro* antiproliferative activity of partially purified *Trigona laeviceps* propolis from Thailand on human cancer cell lines. *BMC Complement Alternat Med* 2011;**11**:30–7.
20. Bankova VS, De Castro SL, Marcucci MC. Propolis: Recent advances in chemistry and plant origin. *Apidologie* 2000;**31**:3–15.
21. Gómez-Caravaca AM, Gómez-Romero M, Arráez-Román D, Segura-Carretero A, Fernández-Gutiárrez A. Advances in the analysis of phenolic compounds in products derived from bees. *J Pharm Biomed Anal* 2006;**41**:1220–34.
22. Moreira LL, Dias T, Dias LG, Rogão M, Da Silva JP, Estevinho LM. Propolis influence on erythrocyte membrane disorder (hereditary spherocytosis): a first approach. *Food Chem Toxicol* 2011;**49**:520–6.
23. Valente MJ, Baltazar AF, Henrique R, Estevinho LM, Carvalho M. Biological activities of Portuguese propolis: protection against free radical induced erythrocyte damage and inhibition of human renal cancer cell growth *in vitro*. *Food Chem Toxicol* 2011;**49**:86–92.
24. Moţ AC, Soponar F, Sârbu C. Multivariate analysis of reflectance spectra from propolis: geographical variation in Romanian samples. *Talanta* 2010;**81**:1010–5.
25. Cardoso S, Ribeiro M, Ferreira IL, Rego AC. Northeast Portuguese propolis protects against staurosporine and hydrogen peroxide-induced neurotoxicity in primary cortical neurons. *Food Chem Toxicol* 2011;**49**:2862–8.

26. Silva JC, Rodrigues S, Feás X, Estevinho LM. Antimicrobial activity, phenolic profile and role in the inflammation of propolis. *Food Chem Toxicol* 2012;**50**:1790–5.
27. Cheng H, Qin ZH, Guo XF, Hu XS, Wu JH. Geographical origin identification of propolis using GC-MS and electronic nose combined with principal component analysis. *Food Res Int* 2013;**51**:813–22.
28. Więckiewicz W, Miernik M, Więckiewicz M, Morawiec T. Review Article: does propolis help to maintain oral health? *Evid Based Complement Alternat Med* 2013;**2013**:1–8.
29. Lu LC, Chen YW, Chou CC. Antibacterial activity of propolis against *Staphylococcus aureus*. *Int J Food Microbiol* 2005;**102**:213–20.
30. Bruschi ML, Dota KFD, Consolaro MEL, Svidzinski TIE. Antifungal activity of brazilian propolis microparticles against yeasts isolated from vulvovaginal candidiasis. *Evid Based Complement Alternat Med* 2011;**2011**:1–8.
31. Schnitzler P, Neuner A, Nolkemper S, Zundel C, Nowack H, Sensch KH, et al. Antiviral activity and mode of action of propolis extracts and selected compounds. *Phytotherapy Research* 2010;**24**:20–8.
32. Moreira L, Dias LG, Pereira JA, Estevinho LM. Antioxidant properties, total phenols and pollen analysis of propolis samples from Portugal. *Food Chem Toxicol* 2008;**46**:3482–5.
33. Libério SA, Pereira AL, Araújo MJ, Dutra RP, Nascimento FR, Monteiro-Neto V, et al. The potential use of propolis as a cariostatic agent and its actions on mutans group streptococci. *J Ethnopharmacol* 2009;**125**:1–9.
34. Szliszka E, Czuba ZP, Domino M, Mazur B, Zydowicz G, Krol W. Ethanolic extract of propolis (EEP) enhances the apoptosis- inducing potential of TRAIL in cancer cells. *Molecules* 2009;**14**:738–54.
35. Orsatti CL, Missima F, Pagliarone AC, Bachiega TF, Búfalo MC, Araújo Jr JP, et al. Propolis immunomodulatory action *in vivo* on Toll-like receptors 2 and 4 expression and on pro-inflammatory cytokines production in mice. *Phytother Res* 2010;**24**:1141–6.
36. Nassar SA, Mohamed AH, Soufy H, Nasr SM, Mahran KM. Immunostimulant effect of Egyptian propolis in rabbits. *Scientific World Journal* 2012;**2012**:1–9.
37. Gekker G, Hu S, Spivak M, Lokensgard JR, Peterson PK. Anti-HIV-1 activity of propolis in CD4+lymphocyte and microglial cell cultures. *J Ethnopharmacol* 2005;**102**:158–63.
38. Chen J, Long Y, Han M, Wang T, Chen Q, Wang R. Water soluble derivative of propolis mitigates scopolamine-induced learning and memory impairment in mice. *Pharmacol Biochem Behav* 2008;**90**:441–6.
39. Yildirim Z, Hacievliyagil S, Kutlu NO, Aydin NE, Kurkcuoglu M, Iraz M, et al. Effect of water extract of Turkish propolis on tuberculosis infection in guinea-pigs. *Pharmacol Res* 2004;**49**:287–92.
40. Daugsch A, Moraes C, Fort P, Park Y. Brazilian red propolis – chemical composition and botanical origin. *Evid Based Complement Alternat Med* 2008;**5**:435–41.
41. Bravo L. Polyphenols: chemistry, dietary sources, metabolism and nutritional significance. *Nutr Rev* 1998;**56**:317–33.
42. Vinson JA, Hao Y, Su X, Zubik L. Phenol antioxidant quantity and quality in foods: vegetables. *J Agrict Food Chem* 1998;**46**:3630–4.
43. Uthurry CA, Hevia D, Gomez-Cordoves C. Role of honey polyphenols in health. *J ApiProduct ApiMed Sci* 2011;**3**:141–59.
44. Viuda-Martos M, Ruiz-Navajas Y, Fernández-López J, Pérez-Álvarez JA. Functional properties of honey, propolis, and royal jelly. *J Food Sci* 2008;**73**:117–24.
45. Ksouri R, Megdiche W, Debez A, Falleh H, Grignon C, Abdelly C. Salinity effects on polyphenol content and antioxodant activities in leaves of the halophyte *Cakile maritima*. *Plant Physiol Biochem* 2007;**45**:244–9.
46. Küçük M, Kolayli S, Karaoglu S, Ulusoy E, Baltaci C, Candan F. Biological activities and chemical composition of three honeys of different types from Anatolia. *Food Chem* 2007;**100**:526–34.
47. Bansal V, Medhi B, Pandhi P. Honey – a remedy rediscovered and its therapeutic utility. *Kathmandu Univ Med J* 2005;**3**:305–9.
48. Cushnie TPT, Lamb AJ. Detection of galangin-induced cytoplasmic membrane damage in *Staphylococcus aureus* by measuring potassium loss. *J Ethnopharmacol* 2005;**101**:243–8.
49. Fiorani M, Accorsi A, Blasa M, Diamantini G, Piatti E. Flavonoids from Italian multifloral honeys reduce the extracellular ferricyanide in human red blood cells. *J Agric Food Chem* 2006;**54**:8328–34.
50. Ferreira ICFR, Aires E, Barreira JCM, Estevinho LM. Antioxidant activity of Portuguese honey samples: different contributions of the entire honey and phenolic extract. *Food Chem* 2009;**114**:1438–43.

51. Gomes T, Feás X, Iglesias A, Estevinho LM. Study of organic honey from the Northeast of Portugal. *Molecules* 2011;**16**:5374–86.
52. Alvarez-Suarez-Suarez JM, Tulipani S, Diaz D, Estevez Y, Romandini S, Giampieri F, et al. Antioxidant and antimicrobial capacity of several monofloral Cuban honeys and their correlation with color, polyphenol content and other chemical compounds. *Food Chem Toxicol* 2010;**48**:2490–9.
53. Chang X, Wang J, Yang S, Chen S, Song Y. Antioxidative, antibrowning and antibacterial activities of sixteen floral honeys. *Food Funct* 2011;**2**:541–6.
54. Estevinho LM, Feás X, Seijas JA, Vazquez-Tato MP. Organic honey from Trás-Os-Montes region (Portugal): chemical, palynological, microbiological and bioactive compounds characterization. *Food Chem Toxicol* 2012;**50**:258–64.
55. Guerrini A, Bruni R, Maietti S, Poli F, Rossi D, Paganetto G, et al. Ecuadorian stingless bee (Meliponinae) honey: a chemical and functional profile of an ancient health product. *Food Chem* 2009;**114**:1413–20.
56. Candiracci M, Citterio B, Diamantini G, Blasa M, Accorsi A, Piatti E. Honey flavonoids, natural antifungal agents against *Candida albicans*. *Int J Food Prop* 2011;**14**:799–808.
57. Soler C, Gil M, García-Viguera C, Tomás-Barberán FA. Flavonoid patterns of French honeys with different floral origin. *Apidologie* 1995;**26**:53–60.
58. Vit P, Soler C, Tomás-Barberán FA. Profiles of phenolic compounds of *Apis mellifera* and *Melipona* spp honeys from Venezuela. *Eur Food Res Technol* 1997;**204**:43–7.
59. Miguel MG, Nunes S, Dandhlen SA, Cavaco AM, Antunes MD. Phenols and antioxidant activity of hydroalcoholic extracts of propolis from Algarve, South of Portugal. *Food Chem Toxicol* 2010;**48**:3418–23.
60. Bankova V, Popova M, Bogdanov S, Sabatini A. Chemical composition of European propolis: Expected and unexpected results. *Zeitschrift für Naturforschung, Teil C* 2002;**57**:530–3.
61. Banskota AH, Tezuka Y, Adnyana IK, Ishii E, Midorikawa K, Matsushige K, et al. Hepatoprotective and anti-*Helicobacter pylori* activities of constituents from Brazilian propolis. *Phytomedicine* 2001;**8**:16–23.
62. Bankova V. Recent trends and important developments in propolis research. *Evid Based Complement Alternat Med* 2005;**2**:29–32.
63. Ahn MR, Kumazawa S, Usui Y, Nakamura J, Matsuka M, Zhu F, et al. Antioxidant activity and constituents of propolis collected in various areas of China. *Food Chem* 2007;**101**:1383–92.
64. Draganova-Filipova MN, Georgieva MG, Peycheva EN, Miloshev GA, Sarafian VS, Peychev LP. Effects of propolis and CAPE on proliferation and apoptosis of McCoy-Plovdiv cell line. *Folia Medica* 2008;**50**:53–9.
65. Liao HF, Chen YY, Liu JJ, Hsu ML, Shieh HJ, Liao HJ, et al. Inhibitory effect of caffeic acid phenethyl ester on angiogenesis, tumor invasion, and metastasis. *J Agric Food Chem* 2003;**51**:7907–12.
66. Chen YJ, Liao HF, Tsai TH, Wang SY, Shiao MS. Caffeic acid phenethyl ester preferentially sensitizes CT26 colorectal adenocarcinoma to ionizing radiation without affecting bone marrow radioresponse. *Int J Radiat Oncol Biol Phys* 2005;**63**:1252–61.
67. Marcucci MC, Bankova VS. Chemical composition, plant origin and biological activity of Brazilian propolis. *Curr Topics Phytochem* 1999;**2**:115–23.
68. Park YK, Alencar SM, Aguiar CL. Botanical origin and chemical composition of Brazilian propolis. *J Agric Food Chem* 2002;**50**:2502–6.
69. Cuesta-Rubio O, Frontana-Uribe BA, Ramırez-Apan T, Cardenas J. Polyisoprenylated benzophenones in Cuban propolis; biological activity of nemorosone. *Zeitschrift für Naturforschung* 2002;C57:372–8.
70. Cheung KW, Sze DM, Chan WK, Deng RX, Tu W, Chan GC. Brazilian green propolis and its constituent, artepillin C inhibits allogeneic activated human CD4 T cells expansion and activation. *J Ethnopharmacol* 2011;**138**:463–71.
71. Chan GC-F, Cheung K-W, Sze DM-Y. The immunomodulatory and anticancer properties of propolis. *Clin Rev Allergy Immunol* 2013;**44**:262–73.
72. Silver IA. The physiology of wound healing. In: Hunt TK, ed. *Wound healing and wound infection: theory and surgical practice*. New York: Appleton-Century-Crofts; 1980. pp. 11–28.
73. Molan P. Why honey is effective as a medicine. *Bee World* 2001;**82**:22–40.
74. Blair S, Carter D. The potential for honey in the management of wound and infection. *Australian Infection Control* 2005;**10**:24–31.

75. Irish J, Carter D, Shokohi T, Blair S. Honey has an antifungal effect against *Candida* species. *Med Mycol* 2006;**44**:289–91.
76. Kegels F. Clinical evaluation of honey-based products for lower extremity wounds in a home care settings. *Wounds UK* 2011;**7**:46–53.
77. Smaropoulos E, Romeos S, Dimitriadou C. Honey-based therapy for paediatric burns and dermal trauma compared to standard hospital protocol. *Wounds UK* 2011;**7**:33–40.
78. Dunford C, Cooper R, White RJ, Molan P. The use of honey in wound management. *Nursing Standard* 2000;**15**:63–8.
79. Robson V, Ward RG, Molan PC. The use of honey in split-skin grafting. *10th conference of the european wound management association*. Harrogate, UK; 2000.
80. Betts JA, Molan PC. A pilot trial of honey as a wound dressing has shown the importance of the way honey is applied to wounds. *11th conference of the european wound management association*. Dublin, Ireland; 2001.
81. Natarajan S, Williamson D, Grey JA, Harding KG, Cooper RA. Healing of an MRSA-colonised, hydroxyurea-induced leg ulcer with honey. *J Dermatol Treat* 2001;**12**:33–6.
82. Lu J, Carter DA, Turnbull L, Rosendale D, Hedderley D, Stephens J, et al. The Effect of New Zealand Kanuka, manuka and clover honeys on bacterial growth dynamics and cellular morphology varies according to the species. *PLoS ONE* 2013;**8**:1–12.
83. Al-Waili NS. Investigating the antimicrobial activity of natural honey and its effects on the pathogenic bacterial infections of surgical wounds and conjunctiva. *J Med Food* 2004;**7**:210–22.
84. Al-Waili N, Al-Ghamdi A, Ansari MJ, Al-Attal Y, Salom K. Synergistic effects of honey and propolis toward drug multi-resistant *Staphylococcus aureus, Escherichia coli* and *Candida albicans* isolates in single and polymicrobial cultures. *Int J Med Sci* 2012;**9**:793–800.
85. Al-Waili NS, Saloom KY. Effects of topical honey on post-operative wound infections due to gram positive and gram negative bacteria following caesarean sections and hysterectomies. *Eur J Med Res* 1999;**4**:126–30.
86. Bulman MW. Honey as a surgical dressing. *Middlesex Hosp J* 1953;**55**:188–9.
87. Efem SEE. Clinical observations on the wound healing properties of honey. *Br J Surg* 1988;**75**:679–81.
88. Khristov G, Mladenov S. Honey in surgical practice: the antibacterial properties of honey. *Khirurgiya* 1961;**14**:937–45.
89. Hamdy MH, El-Banby MA, Khakifa KI, Gad EM, Saven EM. *The antimicrobial effect of honey in the management of septic wounds. Proc 4th int conf on apiculture in tropical climates*, vol. **56**. El Cairo, International Bee Research Association; 1988.
90. Vardi A, Barzilay Z, Linder N, Cohen HA, Paret G, Barzilai A. Local application of honey for treatment of neonatal postoperative wound infection. *Acta Paediatrica* 1998;**87**:429–32.
91. Subrahmanyam M. A prospective randomized clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns* 1998;**24**:157–61.
92. Radwan SS, El-Essawy AA, Sarhan MM. Experimental evidence for the occurrence in honey of specific substances active against microorganisms. *Zentralbl Mikrobiol* 1984;**139**:249–55.
93. Gethin G, Cowman S. Manuka honey vs. hydrogel – a prospective, open label, multicenter, randomized controlled trial to compare de-sloughing efficacy and healing outcomes in venous ulcers. *J Clin Nurs* 2008;**10**:1365–2702.
94. Molan PC. The role of honey in the management of wounds. *J Wound Care* 1999;**8**:423–6.
95. Shimizu T, Takeshita Y, Takamori Y, Kai H, Sawamura R, Yoshida H, et al. Efficacy of Brazilian propolis against Herpes Simplex Virus type 1 infection in mice and their modes of antiherpetic efficacies. *Evid Based Complement Alternat Med* 2011;**2011**:1–9.
96. Oksuz H, Duran N, Tamer C, Cetin M, Silici S. Effect of propolis in the treatment of experimental *Staphylococcus aureus* keratitis in rabbits. *Ophtalmic Res* 2005;**37**:328–34.
97. Onlen Y, Duran N, Atik E, Savas L, Altug E, Yakan SA, et al. Antibacterial activity of propolis against MRSA and synergism with topical mupirocin. *J Altern Complement Med* 2007;**13**:713–8.
98. Sforcin JM, Bankova V. Propolis: Is there a potential for the development of new drugs? *J Ethnopharmacol* 2011;**133**:253–60.
99. Orsi RO, Sforcin JM, Funari SRC, Fernandes Jr A, Bankova V. Synergistic effect of propolis and antibiotics on the Salmonella Typhi. *Br J Microbiol* 2006;**37**:108–12.

100. Orsi RO, Fernandes A, Bankova V, Sforcin JM. The effects of Brazilian and Bulgarian propolis *in vitro* against Salmonella Typhi and synergism with antibiotics acting on the ribosome. *Nat Prod Res* 2012;**26**:430–7.
101. Sehn E, Hernandes L, Franco SL, Gonçalves CCM, Baesso ML. Dynamics of reepithelialisation and penetration rate of a bee propolis formulation during cutaneous wounds healing. *Anal Chim Acta* 2009;**635**:115–20.
102. Gregory SR, Piccolo N, Piccolo MT, Heggers JP. Comparison of propolis skin cream to silver sulfadiazine: a naturopathic alternative to antibiotics in treatment of minor burns. *J Alternat Complement Med* 2002;**8:**77–83.
103. Fearnley J. *Bee propolis: natural healing from the hive using propolis to treat disease*. London: Souvenir Press; 2001.
104. Andriţoiu CV, Prisăcaru AI, Andriescu C, Popa IM. Evaluation of the efficacy of some bee products upon the chemically induced cutaneous erythema in Wistar rats. *Ann Roman Soc Cell Biol* 2012;**17**:258–64.
105. Molan PC. The potential of honey to promote oral wellness. *Gen Dent J* 2001;**49**:584–9.
106. Molan PC, Betts JA. Clinical usage of honey as a wound dressing: an update. *J Wound Care* 2004;**13**:353–6.
107. Vlcekova P, Krutakova B, Takac P, Kozanek M, Salus J, Majtan J. Alternative treatment of gluteofemoral fistulas using honey: a case report. *Int Wound J* 2012;**9**:100–3.
108. Abdelmonem AM, Rasheed SM, Mohamed AS. Bee-honey and yogurt: a novel mixture for treating patients with vulvovaginal candidiasis during pregnancy. *Arch Gynecol Obstet* 2012;**286**:109–14.
109. Agbagwa OE, Frank-Peterside N. Effect of raw commercial honeys from Nigeria on selected pathogenic bacteria. *Afr J Microbiol Res* 2010;**4**:1801–3.
110. Chauhan A, Pandey V, Chacko KM, Khandal RK. Antibacterial activity of raw and processed honey. *Electronic J Biol* 2010;**5**:58–66.
111. Sherlock O, Dolan A, Athman R, Power A, Gethin G, Cowman S, et al. Comparison of the antimicrobial activity of ulmo honey from Chile and manuka honey against methicillin-resistant *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. *BMC Complementary Altern Med* 2010;**10**:1–5.
112. Hassanein SM, Gebreel HM, Hassan AA. Honey compared with some antibiotics against bacteria isolated from burn wound infections of patients in Ain Shams University hospital. *J Am Sci* 2010;**6**:301–20.
113. Cernak M, Majtanova N, Cernak A, Majtan J. Honey prophylaxis reduces the risk of endophthalmitis during perioperative period of eye surgery. *Phytother Res* 2012;**26**:613–6.
114. Shahzad A, Cohrs RJ. *In vitro* antiviral activity of honey against varicella zoster virus (VZV): a translational medicine study for potential remedy for Singles. *Translational Biomedical* 2012;**3**:1–7.
115. Haffejee IE, Moosa A. Honey in the treatment of infantile gastroenteritis. *Br Med J* 1985;**290**:1866–7.
116. Linnett P. Honey for equine diarrhea. *Control Therapy* 1996;**906**.
117. Dooley CP, Cohen H. The clinical significance of *Campylobacter pylori*. *Ann Intern Med* 1989;**108**:70–9.
118. Hejase MJ, Simonin JE, Bihrle R, Coogan CL. Genital Foumier's gangrene: experience with 38 patients. *Urology* 1996;**47**:734–9.
119. Burlando F. Sull'azione terapeutica del miele nelle usdoni. *Minerva Dennatologica* 1978;**113**:699–706.
120. Koo H, Gomes BPFA, Rosalen PL, Ambrosano GMB, Park YK, Cury JA. *In vitro* antimicrobial activity of propolis and *Arnica montana* against oral pathogens. *Arch Oral Biol* 2000;**45**:141–8.
121. Santos FA, Bastos EMA, Uzeda M, Carvalho MAR, Farias LM, Moreira ESA, et al. Antibacterial activity of Brazilian propolis and fractions against oral anaerobic bacteria. *J Ethnopharmacol* 2002;**80**:1–7.
122. Feres M, Figueiredo LC, Barreto IM, Coelho MH, Araujo MW, Cortelli SC. *In vitro* antimicrobial activity of plant extracts and propolis in saliva samples of healthy and periodontally-involved subjects. *J Int Acad Periodontol* 2005;**7**:90–6.
123. Koru O, Toksoy F, Acikel CH, Tunca YM, Baysallar M, Uskudar Guclu A, et al. *In vitro* antimicrobial activity of propolis samples from different geographical origins against certain oral pathogens. *Anaerobe* 2007;**13**:140–5.
124. Tanasiewicz M, Sucha-Nowak M, Dawiec M, Król W, Skaba D, Twardawa H. Influence of hygienic preparations with a 3% content of ethanol extract of brazilian propolis on the state of the oral cavity. *Adv Clin Exp Med* 2012;**21**:81–92.
125. Pereira EMR, Da Silva JLDC, Silva FF, De Luca MP, Ferreira EF, Lorentz TCM, et al. Clinical evidence of the efficacy of a mouthwash containing propolis for the control of plaque and gingivitis: a phase II study. *Evid Based Complement Alternat Med* 2011;**2011**:1–7.
126. Sonmez S, Kirilmaz L, Yucesoy M, Yücel B, Yilmaz B. The effect of bee propolis on oral pathogens and human gingival fibroblasts. *J Ethnopharmacol* 2005;**102**:371–6.

127. De Moura SAL, Negri G, Salatino A, Lima LDC, Dourado LPA, Mendes JB, et al. Aqueous extract of Brazilian green propolis: primary components, evaluation of inflammation and wound healing by using subcutaneous implanted sponges. *Evid Based Complement Alternat Med* 2011;**2011**:1–8.
128. Orsolic N, Basic I. Immunomodulation by water-soluble derivative of propolis: a factor of antitumor reactivity. *J Ethnopharmacol* 2003;**84**:265–73.
129. Moura SAL, Negri G, Salatino A, Lima LDC, Dourado LPA, Mendes JB, et al. Aqueous extract of Brazilian green propolis: primary components, evaluation of inflammation and wound healing by using subcutaneous implanted sponges. *Evid Based Complement Alternat Med* 2009;**2011**:1–9.
130. Tani H, Hasumi K, Tatefuji T, Hashimoto K, Koshino H, Takahashi S. Inhibitory activity of Brazilian green propolis components and their derivatives on the release of cys-leukotrienes. *Bioorg Med Chem* 2010;**18**:151–7.
131. Russo A, Troncoso N, Sanchez F, Garbarino JA, Vanella A. Propolis protects human spermatozoa from DNA damage caused by benzo[a]pyrene and exogenous reactive oxygen species. *Life Sci* 2006;**78**:1401–6.