

Nature treasure: *Aloe vera* and Bee-products

Amal Kabbash, Mona El-Aasr, Fotouh R Mansour, Megumi Hasegawa, Suzuka Ataka, Akira Yagi

Amal Kabbash, PhD., Professor of Pharmacognosy, Faculty of Pharmacy, Tanta University, Egypt

Mona El-Aasr, PhD., Associate professor of Pharmacognosy, Faculty of Pharmacy, Tanta University, Egypt

Fotouh R Mansour, PhD., Lecturer of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Tanta University, Egypt

Megumi Hasegawa, Pharmacist, Grace Meg Salon, Toshima-ku, Tokyo, Japan

Suzuka Ataka, PhD., MD., Assistant professor, Department of Neurology, Osaka City University Medical School, Japan

Akira Yagi, PhD., Editor in-Chief of Journal of Gastroenterology and Hepatology Research, Emeritus professor, Fukuyama University, Hiroshima, Japan

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Akira Yagi, Editor-In-Chief, 2-10-1 Hanagaura, Kasuya-machi, Kasuya-gun, Fukuoka-ken, Japan 811-2310.

Email: akirayagi@nexyzbb.ne.jp

Telephone: +81-92-938-2717

Fax: +81-92-938-2717

Received: July 8, 2018

Revised: July 23, 2018

Accepted: July 24, 2018

Published online: August 21, 2018

ABSTRACT

Based on the standpoint of natural treasure: *Aloe vera* and bee-products, we presented the following information: (i) cardiovascular activity, (ii) usefulness to benign prostatic hyperplasia, chronic

prostatitis, and menopausal syndromes, (iii) enhancement of muscle performance in athletes, (iv) others *in vivo* therapeutic effects, (v) side effects, and (vi) honey, (vii) response of chronic fatigue subjects to the ingestion of *Aloe vera* juice (AVJ) with or without bee-products (propolis and pollen), and case reports, (viii) future prospective, and (ix) summary. The efficacies of AVJ ingestion with bee-products supplement were demonstrated in questionnaire assessments: response of AVJ with bee products ingestion to chronic fatigue subjects. The results provided new possibilities for incorporation of bee-products with AVJ as quality of life-food stuffs. Furthermore, case reports of AVJ with bee-products to patients in metabolic syndrome and inflammation around the under-rectum in ulcerative colitis were demonstrated. Ingestion of *Aloe vera* juice with bee-products supplement could provide the noteworthy improvement.

Key words: Nature treasure: *Aloe vera*; Bee products; Pollen; Propolis; Honey; Possible therapeutic effect; Questionnaire assessment; Case reports

© 2018 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Kabbash A, El-Aasr M, Mansour FR, Hasegawa M, Ataka S, Yagi A. Nature treasure: *Aloe vera* and Bee-products. *Journal of Gastroenterology and Hepatology Research* 2018; 7(4): 2612-2631 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2357>

INTRODUCTION

The studies on human body-friendly natural products have been researched because the abuse and side effect of chemicals^[1]. Treatment with bees and their products has ancient origins. Recently, honey and bee-products have a heritage of use as medicine. Today, the virtues of bee-products are extolled by some, especially those interested in alternative and complementary medicines, who describe the use of honey, pollen, propolis, wax, royal jelly and venom for medicinal purposes^[2].

In the last two decades, many papers have been published on issues concerning bee-pollen. Bee-pollen has been used traditionally by humans for religious purpose and as supplementary food. Bee-pollen is a concentrated, energy and vitamin rich food that is not only consumed as a dietary component, but is also used in alternative

medical treatments. Bee-pollen has potential importance as a supplementary and survival food, and for conditioning of athletes^[3]. Some have related to nutritional and therapeutic claims supported by scientific based evidence and many have dealt with quality control and validation of bee-pollen products^[4]. Bee-pollen is the result of the agglutination of flower pollens, made by worker honey bees, with nectar and salivary substances, and collected at the hive entrance^[5]. For centuries the nutritional value of bee-pollen was surrounded by mystery. The old Egyptians describe it as “a life-giving dust”. Some of the “Fathers of Western Medicine” (Hippocrates, Pliny the Elder, and Pythagoras) trusted the healing qualities of bee-pollen; they often prescribed it to their patients^[4]. Bee-pollen constitutes a natural source of antioxidants such as phenolic acids and flavonoids, which are responsible for its biological activity. Recent research has indicated the correlation between dietary polyphenols and cardioprotective, hepatoprotective, anti-inflammatory, antibacterial, anticancerogenic, immunestimulating, antianemic effects, as well as their beneficial influence on osseous tissue. The therapeutic effects of bee-pollen on health result from the presence of phenolic acids and flavonoids which possess anti-inflammatory properties, phytosterol and linolenic acid which play an anticancerogenic role, and polysaccharides which stimulate immunological activity^[5]. Bee-pollen, a bee product of plant origin, varying in its chemical composition, which depends on the flora, presents in various climate zones^[6]. Over 250 biologically active substances of botanic origin have been isolated from bee-pollen, therefore, it constitutes a rich source of biologically active substances^[7]. Polyphenols are components of flower bee-pollen that determine its antioxidative activity^[8-10]. Their content amounts to 3%-5% and may vary significantly depending on the origin of the pollen^[11]. According to the structure of polyphenol compounds in bee-pollen, they can be differentiated into flavonoids and phenolic acids^[5]. Phenolic acids are bioactive components of pollen. Their content in bee-pollen amounts an average to 0.19%. They constitute a group of varied structures and properties. Among them, we can differentiate benzoic acids, phenylacetic acids and cinnamic acids. The derivatives of cinnamic and benzoic acids are of the greatest significance due to their effective antioxidant activity which is determined by the number of hydroxyl groups, the placement of functional groups, and any steric effects caused by them^[5,12]. The most common phenolic acids are chlorogenic, gallic, ferulic, cinnamic^[13,14] and caffeic acids^[15], as well as hydroxycinnamic, ortho-coumaric and para-coumaric acids^[9,13,14]. In phenolic compounds present in pollen, the following phenylpropanoids^[8] and derivatives of benzoic acid were determined: 3, 4-dihydroxybenzoic acid, 4-hydroxybenzoic and vanillic acids^[15,16], and 4-hydroxybenzoic acid ethyl ester^[15]. Flavonoids constitute the most significant group of compounds among polyphenols present in bee-pollen. During research on the chemical composition of pollen, various forms and types of flavonoids were identified. Seven groups of flavonoids are distinguished because of their chemical structure: flavones, flavonols, flavanones, flavanes, anthocyanidins, isoflavones, and chalcones. Flavonoids are present in pollen mainly in the form of glycosides, among which flavonol glycosides are present in greatest amounts^[9,15,17,18]. The main flavonols of bee-pollen are quercetin and kaempferol, as well as their glycosides^[9,13,15,19-21]. However, the presence of particular flavonoids in pollen loads differs depending on plant species from which pollen comes^[17,22]. Considering its nutritional value, bee-pollen is primarily a source of nutritious protein^[8,23,24]. Its protein content amounts an average to 23.9% of the product dry mass^[14]. The protein can play an important role for covering the required daily intake. Only about 1/10 of the total protein comes from free amino acids. Pollen contains all essential

amino acids. However, protein content depends strongly on the botanical origin of honey, while the qualitative pattern of the amino acids is similar in the different types of pollen^[25]. Pollen is also a rich source of carbohydrates and lipids. The carbohydrates content are mainly polysaccharides like starch and cell wall material^[26]. The sugars: fructose, glucose and sucrose comprise about 90 % of all low molecular sugars^[27]. There are considerable differences of the fat content and composition of pollen depending on the botanical origin. The differences of fat content are due to the different botanical origin of pollen. In one study, 3% of the total lipids are free fatty acids, about half of them are the unsaturated acids oleic, linoleic (omega-6) and linolenic (omega-3)^[26]. The α -linoleic acid is omega-3 acid, has many beneficial effects in nutrition and health^[28]. Bee-pollen contains also minerals and trace elements, the main mineral is potassium. The mineral levels in pollen were also found to vary considerably in the course of the year due to differences in the floral origin of the pollen. This was true for potassium, magnesium, calcium, manganese and iron, while the zinc and copper content of pollen appeared to be more constant^[29]. The sodium content of pollen is relatively lower, values were found varying between 28 and 93 mg/100 g^[30-33]. There is a significant nutritional and health contribution from vitamins present in pollen: provitamine A, ascorbic acid, tocopherol, thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, folic acid, biotin^[34]. Pollen contains significant amount of carotenoids, mainly β -carotene, which represents about 17% of the totals carotenoids^[32]. Coenzym Q was detected in pollen from China in quantities from 0 to 193 mg/kg^[35].

Propolis is a resinous substance that bees collect from the exudates of plants and forms a part of traditional medicine since ancient times^[36]. Propolis has received attention as a multi-functional natural substance for the effects of physiological control such as anti-inflammatory, anti-microbial, antiviral, antioxidant and anti-cancer effects^[37-41]. Moreover, it has been reported that propolis may help to prevent obesity and hyperglycemia. Propolis contains physiological control components such as polyphenols (flavonoids and phenolic acid conjugate), terpenes and octacosanol. Chemical analysis has pointed to the presence of at least 300 compounds in its composition^[42]. It is mainly composed of resin (50%), wax (30%), essential oils (10%), pollen (5%), and other organic compounds (5%)^[43]. Such as phenolic compounds and esters, flavonoids in all their forms (flavonols, flavones, flavonones, dihydroflavonols, and chalcones), terpenes, β -sitosterols, aromatic aldehydes and alcohols, sesquiterpenes, and stilbene terpenes are identified^[44,45]. Caffeic acid phenethyl ester is a biologically active ingredient of propolis with several interesting biological properties, including apoptosis, metastasis, and radiation sensitivity of cancer cells^[46-48].

Honey is a remarkable, complex natural liquid reported to contain at least 181 substances^[49]. The supersaturated solution consists of fructose (38%) and glucose (31%) as the major constituents, whereas the rest of the solution's composition is constituted by minor constituents such as phenolic acids, flavonoids, ascorbic acid, certain antioxidant enzymes such as glucose oxidase and catalase, carotenoid-like substances, organic acids, and Maillard reaction products^[50]. The minor constituents are reported to be mainly responsible for the antioxidant properties of honey^[51]. It is used for millennia as both food and medicine, honey has been associated with improved antioxidant capacity, modulation of the immune system, antimicrobial activities, influence on lipid values (through antihypercholesterolemic effects) and regulation of glycemic responses, among other benefits^[52]. Honey itself is a unique compound because of its highly variable composition, which depends

on its floral source, although other factors such as environment, season, and processing may also have significant effects on the composition of honey^[53]. Oral administration of *Aloe vera* and honey improves the host body composition and modulates proteolysis through reduction of tumor progression and oxidative stress in rats^[54].

The potential biological activities of *Aloe vera* have been demonstrated. *Aloe vera* inner leaf latex and rind contain many complex organic compounds such as chromones, flavonoids and anthraquinones. Some of these molecules have significant anti-inflammatory activity. Unique aloe pectin, lectin and protein having important properties, have been isolated from the mesophyll cell wall gel. *Aloe vera* leaf gel and its major storage acemannan, had immuno-stimulatory and anti-viral properties. In addition, protein and/or lectin from *Aloe vera* gel, were fully expected as putative prophylactic and biological response modifiers in the treatment of a broad range of inflammatory diseases such as rheumatoid arthritis^[55]. In one study, *Aloe vera* high molecular fractions, such as polysaccharide (acemannan) and glycoprotein (verectin), showed immunomodulatory and anti-inflammatory activities as biogenic stimulant^[56]. The therapeutic efficacy of *Aloe vera* high molecular fractions for treatment of hepatic fibrotic, type 2 diabetic, bed sores and lichen planus patients, and the possible beneficial uses by long-term treatment has been reported^[57,58]. *Aloe vera* supplementation may provide the efficacy of hypoglycemic activity as well as lowering lipid oxidation, and the possible putative prophylaxes to optimize cognitive decline in older adults with pre-diabetes symptom. Anti-oxidative phytochemicals and acemannan in *Aloe vera* has been also contributed to the improvement of health by preventing of age-related diseases and slowing aging processes through their synergistic systems^[59]. Recent technology to study the gut microbiota has defined new milestones for understanding the microbial ecology of the gastrointestinal ecosystem and assessing how the microbial world within us impacts our everyday life. A noble immune-enhancing polysaccharides and the importance of gut microbiota inducing gut immunity were investigated on the basis of applying *Aloe vera* as a dietary supplement^[60-62].

Considering the wide interest generated since ancient times by the medicinal and nutritional properties associated with bee products and *Aloe vera*, the objective of this review article is to summarize the main benefits attributed to the intake of natural bee products with or without *Aloe vera*, with a special focus on the effects exerted on cardiovascular activity, usefulness to benign prostatic hyperplasia and chronic prostatitis, enhancement of muscle performance in athletes, other *in vivo* therapeutic studies of bee-products (bee-pollen and bee-propolis), and side effects. A survey of a large number of adults on investigation of *Aloe vera* juice (AVJ) ingestion alone or with bee-products was comparatively conducted by filling out a questionnaire, and the results of questionnaire totaling in a large number of volunteers were summarized in Table 1, 2, and 3. Figure 1 shows

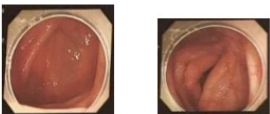
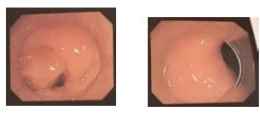
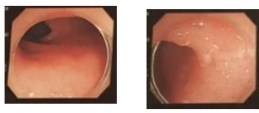
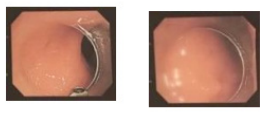
Table 1 Response of chronic fatigue subjects to Aloe vera juice.

<i>Aloe vera</i> juice	Positive efficacy ratio in single respondent
Fatigue and languid syndrome	119 (23.5%)
Constipation	108 (21.3%)
Skin irritation	88 (17.4%)
A stiff shoulder and muscle pains	77 (15.2%)
A poor blood circulation	70 (13.8%)
Headache	48 (9.4%)

Table 2 Response of chronic fatigue subjects to the ingestion of Aloe vera juice with bee-products (propolis and pollen).

<i>Aloe vera</i> juice with bee-products	Positive efficacy ratio in plural respondents		
	propolis	pollen	propolis and pollen
Fatigue and languid syndrome	1078 (42.7%)	1128 (43%)	1050 (39.2%)
Constipation	930 (36.8%)	967 (36.9%)	980 (36.6%)
Skin irritation	785 (31.1%)	825 (31.5%)	827 (30.9%)
A stiff shoulder and muscle pains	767 (30.4%)	791 (30.2%)	803 (30%)
A poor blood circulation	663 (26.3%)	682 (26%)	694 (25.9%)
Headache	517 (20.5%)	531 (20.2%)	543 (20.3%)

Table 3 Case reports: Daily ingestion of Aloe vera juice (AVJ) and Bee products.

Case 1	Ingestion	HbA1c	BMI	Blood glucose
Male, 68 year, Obesity	AVJ + Bee products, 600 mL/day + 30 g/day, In multi-dose.	Apr. 2003: 12.3; Aug. 2003: 5.2; Sep. 2004: 5.0.	Apr. 2003, 29.0; Aug. 2003, 20.0; Sep. 2004, 20.0.	
Female, 60 year, Obesity	AVJ + Bee products, 600 mL/day + 20 g/day, In multi-dose.	Nov. 2015: 11.0; Apr. 2016: 7.8; Aug. 2016: 6.6.	Neutral Fat: LDL-c: HDL-c Nov. 2015: 90: 140: 61; Apr. 2016: 85: 119: 40.	Nov. 2015: 310.0; Apr. 2016: 127.0; Aug. 2016: 110.0.
Case 2 Female, 36 year, Ulcerative, Colitis (UC)	AVJ + Bee products, 600 mL/day + 20 g/day, In multi-dose.	Colonoscopy: Dec. 7, 2016--- Feb. 25, 2017		
		Before, UC diagnosis	After, Remission	
				
				

Case 1: Daily combined ingestion of aloe vera juice (AVJ) 600 mL and Bee products 20-30 g (bee-pollen and propolis) in multi-dose provided a potent improvement of metabolic syndrome, decreasing HbA1c value, BMI and blood glucose content. Case 2: Inflammation was detected with colonoscopy around under-rectum. Dairy combined digestion, 600ml AVJ and Bee products 20g in multi-dose clearly remitted inflammation around the under-rectum as shown on photography after three months. These case reports suggested that daily intake of AVJ and bee products supplement effectively prevents obesity and ulcerative colitis without any side effect.

“Response of AVJ with or without bee-products to the subjects with health troubles”.

CARDIOVASCULAR ACTIVITY

There is an increase in global demand for safe and effective natural products that confer free radical scavenging activities and that offer protection against oxidative stress induced cardiovascular diseases. Cardioprotective effects of Tualang honey for amelioration of cholesterol and cardiac enzymes levels were studied^[63].

Tualang honey had the highest content of phenolics and flavonoids, as well as the best free radical scavenging properties^[64,65]. The cardioprotective effects of Malaysian Tualang honey against isoproterenol-induced myocardial infarction in rats were studied by investigating changes in the levels of cardiac marker enzymes, cardiac troponin I, triglycerides, total cholesterol, lipid peroxidation products, and antioxidant defense system. Pretreatment of ischemic

rats with Tualang honey conferred significant protective effects on the biochemical parameters. The results of this study demonstrated that Tualang honey provide cardioprotective effects on isoproterenol-induced oxidative stress by enhancing endogenous antioxidant enzyme activity through inhibition of lipid peroxidation^[63].

Changes in the cardiovascular parameters of Wistar-Kyoto rats and spontaneously hypertensive rats were examined following a 4-week diet of Brazilian propolis. This resulted in significant reductions in systolic blood pressure in hypertensive rats. Experiments using aorta isolated from animals fed a diet of propolis revealed increased acetylcholine induced relaxation in hypertensive rats. The results suggested that propolis produces an antihypertensive effect that may be mediated by potentiation of acetylcholine-induced vasodilatation^[66,67]. The effects of a subtype of Brazilian propolis, the Red propolis, in adult male Wistar rat models were studied. The rats were divided into untreated and red propolis-treated groups, after 30 days of surgery; when rats already exhibited

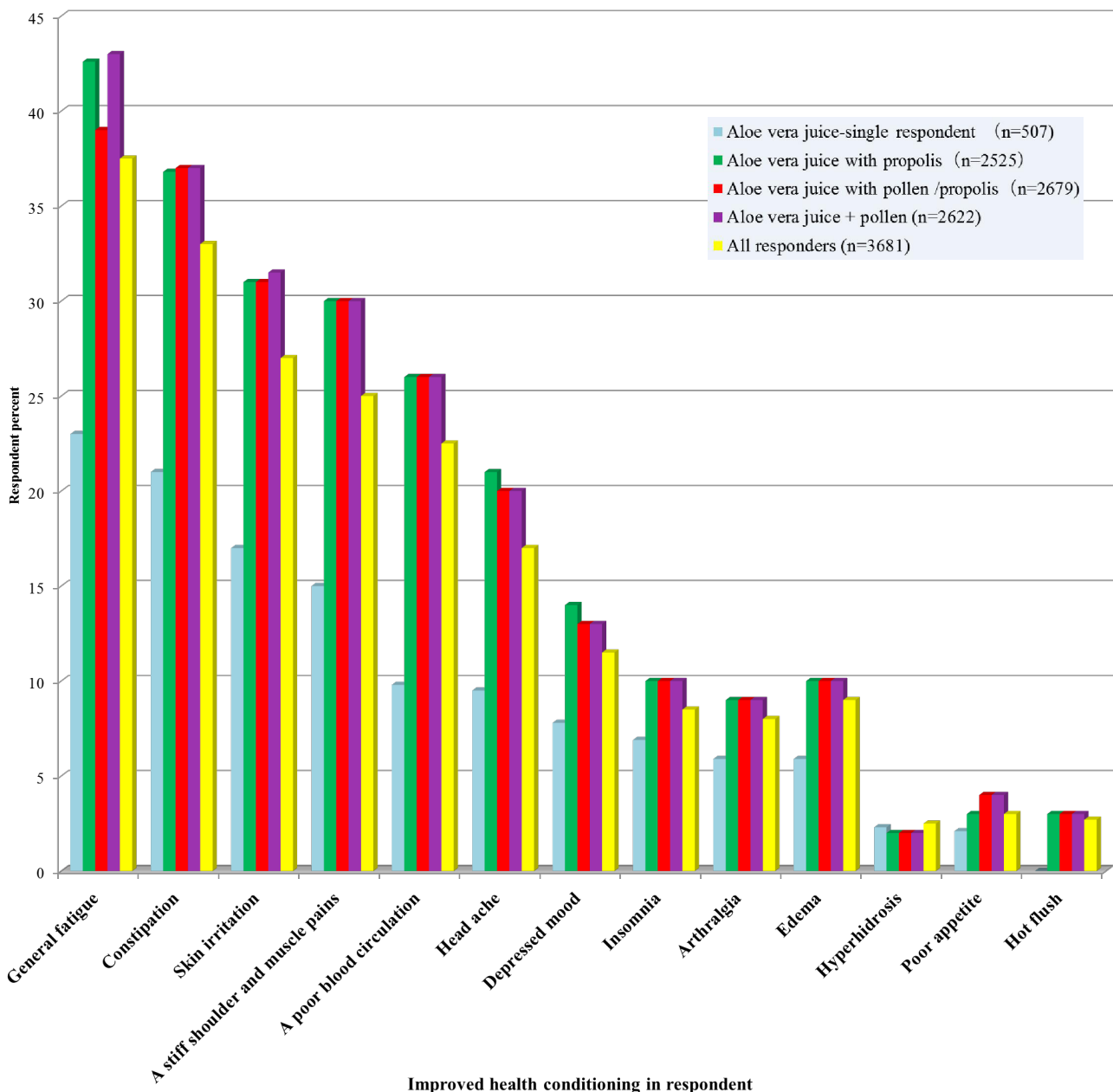


Figure 1 Response of Aloe vera juice with Bee-products (pollen/propolis).

marked hypertension and proteinuria, animals were observed for 90 days from the surgery day. Red propolis-treated groups showed significant reduction of hypertension and oxidative stress^[68]. Mishima *et al.*, demonstrated a significant reduction in blood pressure of spontaneously hypertensive rats when treated with propolis extracts rich in caffeoylquinic acids^[69]. In another study using isolated rat aorta, Cicala *et al.*, demonstrated that the addition of caffeic acid, a major component of propolis found in Asia and Europe, inhibited the vasoconstrictor response to phenylephrine and potassium chloride^[70]. Propolis flavonoids derivatives as dihydrokaempferide, betuletol and especially isosakuranetin, also demonstrated antihypertensive effect in spontaneously hypertensive rats^[66,71]. Chemical composition of alcoholic red propolis extract employed in this study was: 20% of red propolis; 27% distilled water and 53% ethanol. The main constituents of red propolis extract were isoflavonoids; medicarpin and 3-hydroxy-8, 9 dimethoxypterocarpan which represented more than 60% of its composition^[67]. Previous observations also suggested the involvement of oxidative stress in the pathogenesis of hypertension^[72-75]. One of the proposed mechanisms is the interaction between oxidative stress and the renin angiotensin aldosterone system, as the mesangial cells stimulated with angiotensin II could produce superoxide anions^[74]. Red propolis-treated groups in this study, showed significant reduction of oxidative stress^[68].

Furthermore, treatment of patients with arterial hypertension was studied by Liferov *et al.*, using bee pollen. The treatment involved 57 patients (men and women) for 45 days by intake of 15 g of bee bread twice daily. Total cholesterol decreased by 24%, LDL by 36%, and HDL increased by a factor of 2.1^[76]. Koslic and Takac have studied the effect of intake 2.5 g pollen two times on five arteriosclerosis patients with increased triglyceride content. Measurement of triglyceride content, lipoproteins and cholesterol in blood after two weeks showed that triglyceride content fell to half the initial values, while changes in the levels of lipoproteins and cholesterol were not significant^[77]. Georgieva and Wassilev studied the effect of bee-pollen on 60 elderly patients with arteriosclerosis and 40 with brain arteriosclerosis. The patients were given one tablespoon pollen before meals, twice a day for one month. A small fall of cholesterol and lipoproteins in arteriosclerosis patients and improvement of non dynamic neurasthenia disorders of brain arteriosclerosis patients were observed^[78]. Treatment of adult patients with dyslipidemia using bee-pollen has been reported. Intake of 40 g daily pollen or bee bread for 12 weeks resulted in cholesterol decrease by 11.4 and 20.5% respectively; the same quantity of bee bread decreased triglycerides by 12.5% and HDL by 14.3%. Furthermore, another study designed for treatments of adult patients with dyslipidemia used 4.5 g pollen for 30 days, resulted in a decrease of cholesterol and β -lipoprotein, there was a decrease in these parameters in smoking women by 30.8 and 12.8%, respectively^[79].

Polanski M. *et al.*, have evaluated the biochemical and morphological effects of hydrophilic pollen extract (HPE) in adrenaline-induced myocardial damage. The study was carried out using 40 Wistar rats. The first group was intoxicated with adrenaline at a dose of 100 μ g/kg i. p. The second group was given simultaneously HPE and adrenaline. The third group consisted of control animals. Biochemical analysis and histological were performed after 24 hours of the experiment. The activity of SGOT, CPK and AP was determined. Cellular infiltration of the endocardium, microfocal myocyte damage, wavy myofibers, cellularity of the stroma and perivascular infiltrates were evaluated. The results of this study revealed that the levels of SGOT and CPK were significantly higher in the first group than in other tested groups.

Histological examination also revealed marked differences among these groups, confirming cardioprotection by HPE^[80].

Another study reported that fifty-five postmenopausal women were treated with the food supplement Melbrosia [a combination of flower pollen, perga (fermented flower pollen), and royal jelly] for 3 months. The blood levels of high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TG), total cholesterol (TC), vascular cell adhesion molecule-1 (VCAM-1), and C-reactive protein (CRP) levels were determined. The results showed that treatment with Melbrosia significantly reduced TC and LDL and significantly elevated HDL and TG. There were nonsignificant changes of serum VCAM-1 and CRP levels in patients treated with Melbrosia^[81].

USEFULNESS TO BENIGN PROSTATIC HYPERPLASIA, CHRONIC PROSTATITIS AND MENOPAUSAL SYNDROMES

Benign prostatic hyperplasia (BPH) is a major problem for the patient, the urologist, and health care systems. Medical treatment of BPH is presently dominated by α -adrenoceptor blockers but plant extracts are used extensively in a number of countries. Although plant extracts may not effectively alter the natural history of clinical BPH, their use is valuable in patients with mild symptoms in a number of patients. Plant extracts are inexpensive and have virtually no side effects^[82,83]. Among plant extracts Cernilton, the Gramineae flower pollen extract, is an interesting product. Results of clinical studies using patients with BPH treated with Cernilton have demonstrated a marked reduction in residual urine, prostate volume, and improvement in the rate of urinary flow^[84]. The anticongestive effect of Cernilton leads to a marked reduction in prostate volume^[85]. The anticongestive action of Cernilton is based on the inhibition of prostaglandin and leukotriene biosynthesis. The inhibition of the arachidonic acid cascade by Cernilton prevents intraprostatic tissue oedema and fibrosis and leads to a significant reduction in clinical symptoms^[84,86]. Cernilton is well tolerated and proved to be effective, and safe^[87]. Whilst prostatectomy remains the "gold standard" for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment appears to be an attractive alternative^[88]. There is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia^[89,90]. Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications, whilst symptomatic improvement and patient satisfaction after the operation appears to be less in those who are only mildly or moderately symptomatic than in those with severe symptoms^[91]. Thus, there may be a place for phytochemicals that are of proven benefit and free of side effects for the treatment of patients with mild or moderate symptoms who are awaiting operation or are unfit for surgery^[88]. A double-blind, placebo-controlled study was carried out for treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract^[88]. The results of the study revealed that there was a statistically significant subjective improvement with pollen extract (69% of the patients) compared with placebo (30%). There was also a significant decrease in residual urine and in the antero-posterior diameter of the prostate on ultrasound. The differences in respect of urine flow rate and voided volume were not statistically significant. It is concluded that pollen extract has a beneficial effect in benign prostatic hyperplasia and may have a place in the treatment of patients with mild or moderate symptoms of outflow obstruction^[88]. A further *in vivo* study was conducted to review the evidence for the clinical effects and safety of the rye-grass pollen extract (Cernilton)

in men with symptomatic BPH. Cernilton, prepared from the rye-grass pollen *Secale cereale*, is one of several phytotherapeutic agents available for the treatment of BPH. It is used by millions of men worldwide and is a registered pharmaceutical product in many countries^[92]. Several *in vitro* studies undertaken to investigate the mechanism of action suggest that Cernilton has antiandrogenic effects^[93], may relax urethral smooth muscle tone and increase bladder muscle contraction^[94], or may act on the α -adrenergic receptors and relax the internal and external sphincter muscles^[95]. Complete assessment of the efficacy and safety of Cernilton in the treatment of mild to moderate BPH was reported and the available evidence suggests that Cernilton is well tolerated and modestly improves subjective urological symptoms^[92]. Evidence-based treatment of chronic prostatitis and chronic pelvic pain syndrome has been difficult because of the heterogeneous patient population in this syndrome^[96]. Although antibiotic treatment is the standard treatment for chronic bacterial prostatitis^[97], a variety of other treatment options are reported, such as phytotherapeutics^[98]. A multicentre, randomized, prospective, double-blind, placebo-controlled phase 3 study was conducted using phytotherapeutics such as pollen extract for treatment of patients with inflammatory chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS), to assess the safety and efficacy of a standardized pollen extract in men with CP/CPPS^[96]. The results of the study showed that treatment of men diagnosed with inflammatory CP/CPPS with pollen extract for 12 weeks resulted in a significantly higher symptom improvement compared to placebo and was well tolerated. This symptom improvement was mainly the result of a significant response in the pain symptomatology, which consequently led to a significant improvement in the total NIH-CPSI score and the QOL subdomain^[96]. NIH-CPSI score is commonly used 13-item questionnaire for the assessment of symptom severity in men with CP/CPPS^[99]. The anti-inflammatory potential associated with cyclo-oxygenase and lipoxygenase inhibition by pollen extract may explain the beneficial for patients with inflammatory CP/CPPS^[100].

Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CNBP/CPPS) is a common health problem among men^[101,102]. The treatment of CNBP/CPPS can be a frustrating challenge to the physician and patient^[103,104]. The efficacy and safety of the pollen extract preparation in the treatment of patients with CNBP/CPPS has been reported. In a double-blind study, 60 patients between 20 and 55 years old with CNBP/CPPS were randomized to receive pollen extract preparation or placebo for 6 months. The patients were evaluated at the start of the treatment and after 6 months of treatment with the help of a symptom questionnaire covering the symptoms in seven pain locations, five voiding symptoms, three storage symptoms, and four sex-related symptoms. The result showed that after treatment for 6 months, patients taking pollen extract were cured or improved than patients taking placebo. The treatment with pollen extract resulted in symptomatic relief of CNBP/CPPS in men^[105]. Experimental data in nonbacterial prostatitis in rats showed that pollen extract fat-soluble fraction protects mainly acinar epithelial cells and inhibits stromal proliferation^[106]. In a further study, a dose-dependent anti-inflammatory action in nonbacterial prostatitis in rats was noted, leading to decreased levels of interleukin-1 α , interleukin-6, and tumor necrosis factor α , which decreases glandular inflammation and might be responsible for the decrease in proliferation and increase of apoptosis seen in the prostate^[107]. Furthermore, the effect of pollen extract, in a dose of 1 tablet three times daily for 6 months for the treatment of chronic prostatitis syndrome and prostatic-dynia was reported in 90 patients. The factors documented before and after treatment were digital

rectal examination of the prostate, uroflowmetry, bacterial studies, leucocyte counts in urine and measurement of complement C3/coeruloplasmin in the seminal fluid, 36% of the patients were cured of their symptoms and signs and 42% improved significantly with an increase in flow rate, a reduction in leukocyturia in post-prostate massage urine and a decrease in complement C3/coeruloplasmin in the ejaculate. Pollen extract was well tolerated by 97% of patients. Patients with complicating factors due to incidental lower urinary tract pathology (e.g. bladder neck sclerosis, urethral stricture or extensive prostatic calcification) failed to respond and a high percentage of these developed bacteriuria^[98]. In addition, pollen extract in association with vitamins provides early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome. A randomized controlled phase III study was designed to assess the safety and efficacy of pollen extract in association with vitamins in males with CP/CPPS. The treatment significantly improved total symptoms, pain and quality of life compared with ibuprofen in patients with CP/CPPS, without severe side-effects^[108]. This improvement is possibly due to the association between the pollen extract and vitamins B₆ and B₁₂ that improve the antioxidant activity of pollen extract with the protective effect on nerves. B vitamins including thiamine (B₁), pyridoxine (B₆) and cyanocobalamin (B₁₂) are capable of anti-nociception in experimental animals with acute and chronic pain evoked by electrical, chemical and thermal stimulation^[109,110]. Several reports have demonstrated that vitamins B₆ and B₁₂ are able to protect neurons from certain injuries^[111,112]. The early improvement of pain relief is due to the protective effect on nerves, and the following improvement in quality of life could be attributed to the antioxidant activity of pollen extract^[109,113].

The polyphenolic content, flavonoid content, and free flavonoid aglycon compounds were determined using gradient reversed phase HPLC. The most predominant compounds were flavonoid glycosides, mainly flavonols. Eighty-two percent of the samples were primarily rutin, quercetin, myricetin, and trans-cinnamic acid as free aglycon. Total phenols were present, at levels of > 0.85 g/100 g in the form of non-tannins, and flavonoids of > 0.35 g/100 g, using spectrophotometric procedures. Rutin is the best identifier of free flavonoid aglycon compounds. A minimum quantity of 200 mg/kg of rutin is suggested to guarantee the nutritional and biological properties required^[114]. Honeybee-collected pollen lumps have attracted interest as a functional food with health benefits. Some studies were carried out to evaluate the effectiveness and safety of honeybee-collected pollen lump extract (HPLE) supplemented food in Japanese patients with outflow obstruction symptoms due to BPH. A double-blind, placebo-controlled clinical trial was performed to investigate the efficacy and safety of honeybee-collected pollen lump extract (HPLE)-supplemented food in 47 patients with benign prostatic hyperplasia (BPH). Outcome measures were the change during 12-week intervention period in subjective symptom scores and 2 urodynamic parameters, maximum flow rate (Q_{max}) and residual urine volume. The results of the study showed substantial subjective and objective improvement with a positive response. There were No HPLE-related health hazards or laboratory abnormalities of clinical significance were encountered^[115].

The effect of different doses of cernilton on preventing the clinical progression of benign prostatic hyperplasia was studied. The results indicated that long-term administration of cernilton at the dose of 750 mg may achieve faster and more obvious efficacy than at 375 mg in improving symptomatic BPH and preventing the clinical progression of BPH, with no adverse events^[116].

The therapeutic efficacy of Cernilton in benign prostatic

hyperplasia patients with histological prostatitis after transurethral resection of the prostate was also evaluated. The results of the study concluded that in BPH patients with histological prostatitis after transurethral resection of the prostate, Cernilton can improve the lower urinary tract symptoms and sexual dysfunction depending on the grade of prostatitis^[117].

Bee-pollen and quality of life in menopausal women

Hot flushes, night sweats, pain during sexual intercourse, hair loss, forgetfulness, depression and sleeping disturbances are common problems among menopausal women and breast cancer patients undergoing antihormonal treatment. Hormone replacement therapy has been claimed to increase the risk of breast cancer has made it relevant to search for new non-hormonal treatments of menopausal symptoms^[118]. The effect of bee-pollen on alleviation of menopausal symptoms in patients receiving tamoxifen and aromatase inhibitors/inactivators was studied. The study compared a pollen-honey mixture with pure honey (placebo) in a prospective, randomized crossover trial in breast cancer patients receiving antihormonal treatment. The menopausal complaints were assessed using the Menopause Rating Scale (MRS). A total of 46 patients were recruited; 68.3% (28/41) of the patients reported an improvement in their symptoms while taking honey, compared with 70.9% (22/31) who reported an improvement with pollen. The results were confirmed by significant improvements in the postmenopausal complaints in the two groups in a pre-post analysis in the MRS and its 3 subscales. The study provided evidence that honey and bee-pollen may improve the menopausal symptoms of breast cancer patients on antihormonal treatment. Of note, honey, which was intended to be used as a placebo, produced similar effects as pollen and they both exceeded the extent of a placebo effect^[119].

It has been reported that an herbal remedy made from pollen extracts, reduces hot flushes and improves quality of life in menopausal women. The pollen extract significantly reduces hot flushes and certain other menopausal symptoms when compared to placebo in a randomized, double-blind, placebo-controlled, parallel trial of 64 menopausal women^[118]. Furthermore, the effect of consumption of bee-pollen on rat ovarian functions was studied. The study aimed to examine the possible effects of bee-pollen added to the feed mixture on rat ovarian functions (secretion activity and apoptosis). The results contributed to new insights regarding the effect of bee-pollen on both secretion activity (release of growth factor IGF-I and steroid hormones progesterone and estradiol) and apoptosis (anti- and pro-apoptotic markers Bcl-2, Bax and caspase-3). Bee-pollen was shown to be a potent regulator of rat ovarian functions^[120].

ENHANCEMENT OF MUSCLE PERFORMANCE IN ATHLETES

Bee-pollen is recommended to enhance athletic performance, reduce the side effects of chemotherapy and improve allergies and asthma.

Laboratory of Government Chemist (LGC) is one of the world leading independent surveillance laboratories providing universal and internationally trusted expertise in all aspects of doping control for sports. Several sport products; *Aloe vera* gel, bee pollen, *etc.*, (Forever living products) had been tested and certified by LGC. LGC has about 50 years' experience in the science of sports doping control (equine, canine, human) and experience of testing within the framework of the world anti-doping agency, and maintains accreditation for testing sports supplements to control contamination with banned substances. This helps athletes to manage the risk of

an inadvertent positive drug test, by choosing supplements that are prepared to the highest quality control standards.

Effects of pollen extract on adolescent swimmers were studied. The study evaluated a variety of physiological parameters using a group ($n = 20$) of adolescent swimmers. During follow up of the study, maximum oxygen uptake increased in both the treatment group and the placebo group, and there were no observable differences between the responses of both groups. Vital capacity showed a significant increase in the treatment group, but not in the placebo group^[121].

Bee-pollen is considered, since memorable times, a good source of nourishing substances and energy. Some of the study conducted on bee pollens revealed that they exhibited antimicrobial, antioxidant and anti-inflammatory activities. The results obtained from these studies demonstrated that bee-pollen possesses good antioxidant activity. There was a correlation between polyphenols, flavonoids and antioxidant activity suggesting that it could be useful in prevention of diseases in which free radicals are implicated^[122-124].

Jérôme Salles *et al.*, have been studied the effect of bee-pollen on the improvement of muscle protein and energy metabolism *in vivo* using rats model. In this study, rats fed with fresh bee pollen-enriched diets showed a significant increase in muscle mass compared to restricted rats. The malnutritionperiod reduced the muscle protein synthesis rate and mTOR/p70S6kinase/4eBP1 activation, and only the 10%-pollen diet was able to restore these parameters. Mitochondrial activity was depressed with food restriction and was only improved by refeeding with the fresh bee pollen-containing diets^[125]. In this study, reduction in muscle protein synthesis was observed in malnourished rats together with a decreased ability to activate the protein translation rate, i.e., decreased activation of the mTOR/p70S6k/4EBP1 signaling pathway. It has been proposed that muscle protein synthesis may be impaired by high concentrations of cytokines during malnutrition^[126]. The reduction in muscle protein synthesis during malnutrition may be explained by an exaggerated inflammatory response. The activity of key mitochondrial enzymes was blunted in malnourished rats, which indicates that the deprivation of energy intake initiated in late-middle-age altered primary mitochondrial function that, in turn, depressed protein turnover in the skeletal muscle. As muscle protein turnover depends on cell energy status, it is tempting to establish a direct link between decreased mitochondrial function, i.e., ATP availability in muscle cells, and a reduced protein synthesis rate. The reduced energy intake may have slowed electron flow through the electron transport chain^[127]. Previous studies have revealed that the therapeutic approaches based on nutrient supplementation, e.g., amino acids, are able to improve muscle protein metabolism^[128]. Therefore, using bee-pollen, which contains high concentrations, not just of amino acids but also other key nutrients, could improve muscle protein metabolism. Fresh bee-pollen contains substantial nutrients that are the factors of anabolic properties. For instance, bee-pollens are rich in essential amino acids, especially leucine, which can impart anabolic properties^[129]. It was reported that leucine supplementation was able to stimulate muscle protein synthesis in a food-deprived rat model^[130]. This effect was mediated by the mTOR signaling pathway. Therefore, the positive action of the 10% fresh bee-pollen-supplemented diet on muscle protein synthesis and mTOR/p70S6k/4EBP1 activation is likely one of the mechanisms of muscle restoral in old malnourished rats. In addition, fresh bee-pollen contains substantial amounts of vitamins, phenolics and phytochemicals and significant quantities of other antioxidant agents^[131]. Marzani *et al.*, assessed the effect of antioxidant supplementation on leucine-regulated protein metabolism in muscles of young and old rats and found that the ability of leucine

to stimulate muscle protein synthesis was significantly decreased in old rats compared with their young counterparts^[132]. Fresh bee-pollen may have a beneficial effect on muscle protein metabolism via a synergistic effect of various nutrients, such as leucine and antioxidants. In addition, some pollen compounds, such as flavone, enhanced the gene and protein expression of Akt, a key intermediate of the insulin signaling pathway, and increased the phosphorylation state, i.e., activation, of insulin receptor- β and Akt in cultured muscle cells^[133]. Insulin is able to increase muscle protein synthesis^[134]. Furthermore, the signaling pathway leading to the stimulation of protein synthesis in muscle cells is shared by leucine and insulin and can be stimulated by both of these mediators^[125].

It has been also reported that fresh pollen refeeding diet triggered an increase in citrate synthase (CS) activity in the plantaris muscle of food-restricted rats. CS is a key enzyme of the Krebs cycle, and beside its functional importance for mitochondria, CS activity also is an index of mitochondrial density^[135,136]. Thus, refeeding with fresh pollen-containing diets appeared to increase mitochondrial biogenesis. Accordingly, complex II and IV activities of the electron transport chain were improved, at least when using the 10% fresh pollen diet. Interestingly, it was proposed that as complex IV activity shows all of the main regulatory mechanisms found in key metabolic enzymes and it is likely represents the rate-limiting step in energy production^[137]. Previous study concluded that fresh bee pollen-supplemented diet-induced improvement in functional mitochondria may be the result of attenuated mitochondrial oxidant emission, increased oxidant scavenging and decreased cellular oxidative damage, all of which could be expected to contribute to maintaining the functional integrity of the mitochondrial machinery^[138]. In conclusion, bee-pollen decreases oxidative damage to tissues^[139] and possesses good anabolic and metabolic activity^[125].

OTHER IN VIVO THERAPEUTIC STUDIES OF BEE-PRODUCTS

Propolis is a resinous substance produced by honey bees, and this substance has been used in folk medicine since ancient times, due to its many biological properties to possess, such as antitumor, antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory effects^[140]. Ishikawa Y. group^[141] investigated the effect of bee-collected pollen (BP) on mast cell activation elicited by the Fc immunoglobulin E (IgE) receptor (Fc epsilon RI)-mediated pathways. The *in vivo* effect of orally administrated BP on cutaneous mast cell activation was examined by passive cutaneous anaphylaxis reaction. *In vitro* mast cell degradation and IgE binding to mast cells and the status of protein tyrosine phosphorylation were examined using bone marrow-derived mast cells. The results revealed that the anti-allergic action of BP was exerted by inhibiting the Fc epsilon RI-mediated activation of mast cells, which plays important roles, not only in the early phase, but also in the late phase of allergic reactions. Artepillin C is the major compound in the Brazilian green propolis from *Baccharis dracunculifolia*. Paulino N. group^[142] investigated the anti-inflammatory effects, absorption, and bio-availability of artepillin C in mice. In HEK 293 cells artepillin C was reduced NF- κ B activity with a mean IC₅₀ of 26 μ g/mL, suggesting anti-inflammatory activity, particularly during acute inflammation. Artepillin C was absorbed after an oral dose (10 mg/kg) with maximal peaks found at 1h (22 μ g/mL). Artepillin C showed anti-inflammatory effects mediated, at least in part, by prostaglandin E2 and nitric oxide inhibition through NF- κ B modulation, and exhibited bio-availability by oral administration. Defects in insulin-stimulated

glucose uptake in skeletal muscle result from the dysfunction of insulin signaling including the phosphatidylinositol-3 kinase pathway and a novel β -arrestin-2-mediated signaling, which leads to insulin resistance (IR). Pollen typhae, a Chinese herb, has been used for long time in traditional Chinese medicine, and has the potential to inhibit the development of IR. The effects of pollen typhae total flavone (PTF) on glucose uptake were investigated to explore the underlying mechanisms in C2C12 myotubes. PTF improved insulin-stimulated glucose uptake in dose- and time-dependent manner in C2C12 myotubes, and prevented palmitate-induced IR. PTF improves insulin-induced glucose uptake via the β -arrestin-2-mediated signaling in C2C12 myotubes^[143]. The effect of bee-pollen *Cistus ladaniferus* extract on ovariectomy (OVX)-induced bone loss *in vivo* was investigated. The water-solubilized extracts were obtained from the bee-pollen of *C. ladaniferus*. *Cistus* extract (5.0 or 10.0mg/100g body weight) was orally administered once daily for 30 days to OVX rats. OVX induced a significant decrease in calcium content in the femoral-diaphyseal and -metaphyseal tissues. This decrease was significantly prevented after the administration of *Cistus* extract (5.0 or 10.0 mg/100g body weight). The study demonstrates that *Cistus* extract has a preventive effect on OVX-induced bone loss *in vivo*^[144]. Furthermore, the calcium content in the femoral-diaphyseal or -metaphyseal tissues was significantly increased in the presence of water-solubilized extract (100 μ g/mL) of *Cistus ladaniferus*, *Fagopyrum esculentum*, *Camellia sinensis* and *Brassica napus*. Alkaline phosphatase activity and DNA content in femoral-diaphyseal or -metaphyseal tissues *in vitro* were significantly increased in the presence of water-solubilized extract obtained from the bee-pollen. The study demonstrates that the extract of bee-pollen has been an anabolic effect on bone components in rats *in vitro* and *in vivo*^[145]. Changes in the cardiovascular parameters of Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR) were examined following a 4-week diet of either Brazilian propolis or *Eucommia uloides* (tochu). A 4-week diet of propolis or tochu resulted in significant reduction in systolic blood pressure in SHR but had no WKY. The results suggest that propolis and tochu produce an anti-hypertensive effect that may be mediated by potentiation of acetylcholine-induced vaso-dilatation^[146]. The effects of ethanol extract of red propolis (EERP) on adipogenesis and evaluated the molecular basis for their anti-obesity effects were investigated. EERP enhanced differentiation of 3T3-L1 cells adipocytes in part by its potency of PPAR α activation and were capable of reversing inhibitory effects of TNF- α on adipocyte differentiation and adiponectin expression. The results suggest the value of EERP as a diet supplement for prevention and treatment of obesity and obesity-associated disorders. Brazilian propolis has multiple biological functions and may help to restore adiponectin expression and insulin sensitivity^[147]. The Brazilian propolis-derived components; artepillin C and its derivative (C3 and C4, respectively) can significantly inhibit TNF- α -mediated downregulation of adiponectin in adipocytes, although they do so via different mechanisms^[148]. The effects of artepillin C, an ingredient of medicinal plant; *Baccharis dracunculifolia*, on adipogenesis and glucose uptake using 3T3-L1 cells were investigated. The results showed that artepillin C promotes adipocyte differentiation and glucose uptake in part by direct binding to PPAR α , which could be the basis of the pharmacological benefits of green propolis intake in reducing the risk of type 2 diabetes. *Baccharis dracunculifolia* is the main botanical source used by honeybees to produce Brazilian green propolis having hepatoprotective properties^[149]. The protective effects of the glycolic extract (propyleneglycol: H₂O; 70: 30) of *B. dracunculifolia* (GEBd) against

oxidative stress in isolated rat liver mitochondria were investigated. GEBd exhibited potent antioxidant activity protecting liver mitochondria against oxidative damage and such action probably contributes to the antioxidant and hepato-protective effects of green propolis^[150]. The Brazilian propolis has the potential to prevent hyperglycemia through the promotion of insulin-sensitive glucose transporter (GLUT)-4-translocation in skeletal muscle and that kaempferide is one of the candidates for active compound in propolis^[151]. The exercise training (70% VO₂max treadmill running exercise for 60min) of 5 times per week for six weeks and the intake (50mg/kg/day) of the water extract from propolis were performed by separating the experimental animals (SD rats, *n* = 32) into CON (*n* = 8) group, CON+Exercise (Ex) group (*n* = 8), Propolis administration: PA group (*n* = 8), and PA+Ex (*n* = 8). PA+Ex group in the skeletal muscle tissue was significantly decreased in comparison with other experimental groups (*p* < 0.05). The parallel treatment of the exercise training and the water extract from propolis can not only increase the use of glycogen of the skeletal muscle and liver tissue, but also it can give the effect to suppress the creation of active oxygen by reducing the activity of the antioxidant enzyme in the body^[152]. The effects of a subtype of Brazilian propolis, the red propolis (RP), in the 5/6 renal ablation model (Nx) were evaluated. RP treatment attenuated hypertension and structural renal damage in Nx model. Animals were observed for 90 days from the surgery day, when Nx+RP group showed significant reduction of hypertension, proteinuria, serum creatinine retention, glomerulosclerosis, renal macrophage infiltration and oxidative stress, compared to age-matched untreated Nx rats, which worsened progressively over time. Reduction of renal inflammation and oxidative stress could be a plausible mechanism to explain this renoprotection^[153]. Artepillin C showed anti-inflammatory effects mediated, at least in part, by prostaglandin E₂ and nitric oxide inhibition through NF-κ B modulation, and exhibited bioavailability by oral administration. Propolis is widely used as an anti-inflammatory raw substance, especially during allergy and airway inflammatory disorders. Brazilian propolis in elderly people may ensure a health promoting action by activating the immune response. A combination therapy (anti-inflammatory drugs plus propolis) in aged adults showed encouraging results^[154]. Critical and less enthusiastic debate about propolis has to be taken into account, due to contradictory results from clinics, respect to *in vitro* and *in vivo* animal evidence. Propoelix™ is a uniquely potent and water-soluble extract of propolis containing high concentrations of anti-inflammatory compounds like caffeic acid phenethyl ester^[155]. A double-blind, randomized, placebo-controlled trial was conducted: sixty-three patients who met the inclusion criteria were enrolled in the trial. Propoelix™ appears to hasten the improvement in platelet counts and TNF-α level and shortens the duration of hospitalization in patients with dengue hemorrhagic fever^[156]. The efficacy of the anti-inflammatory effects of propolis on the systemic and local effects on experimental periodontitis and diabetes was evaluated using fifty-six Wistar rats. The propolis reduced fasting blood glucose levels in diabetes. Propolis might be beneficial as an adjunct treatment of diabetes associated periodontitis and periodontitis without diabetes^[157]. Propolis protects renal tissue against toxicity, free radicals, and other adverse effects induced by diatrizoate. This function is most likely exerted through the antioxidant and antitoxic activities of propolis^[158]. Type 2 diabetes melitus (T2DM) was induced in male Wistar rats using high fat and low dose of streptozotocin. Propolis was administered by oral tubes. Brazilian propolis could beneficial effect in T2DM by increasing tissue PPAR level, restoring serum adiponectin levels, enhancing insulin

sensitivity and subsequently, attenuating elevated glucose level^[159]. Propolis extracts obtained by supercritical extraction (SCO₂) and ethanol extraction were investigated in eight samples of different types of propolis (red, green and brown), collected from different regions in Brazil. The highest concentrations of artepillin C and *p*-coumaric acid were identified in the extracts from SCO₂, indicating a higher selectivity for the extraction of these compounds. It was verified that the composition and biological activity of Brazil propolis vary significantly, depending on the type of sample and geographical area of collection^[160]. The effect of topical application of honey and a mixture of honey, olive oil-propolis extract, and beeswax (HOPE) in treatment of oral mucositis was evaluated. A randomized controlled clinical trial was conducted on 90 patients with acute lymphoblastic leukemia and oral mucositis grades 2 and 3. Generally, in both grades of mucositis, honey produced faster healing than either HOPE or control (*p* < 0.05). Based on the results that showed that honey produced faster healing in patients with grade 2/3 chemotherapy-induced mucositis, the authors recommend using honey and possibly other bee products and olive oil in future therapeutic trials targeting chemotherapy-induced mucositis^[161]. A double blind randomized placebo controlled study assessing propolis (bee glue) efficacy for chemotherapy-induced severe oral mucositis treatment was demonstrated. Severe oral mucositis (OM) was seen in 42% and 48% of patients in the propolis and placebo group, respectively. A new variable model was used as the dependent variable in ANCOVA model, and was not statistically significant between study group (*p* = 0.59). According to the results, propolis cannot be recommended for severe OM treatment^[162]. The effectiveness of a mucoadhesive propolis gel in the prevention of radiation-induced oral mucositis was determined. Twenty-four patients who were selected to undergo radiation therapy for oral cancer were included in this open-label trial (phase II study). They were advised to use a mucoadhesive gel containing propolis 5.0% w/v three times a day starting one day before the course of radiation therapy and concluding after 2 weeks of radiation therapy. Mucoadhesive propolis gel could be considered as a potential topical medication for preventing radiation-induced oral mucositis^[163]. Hand excavation alone does not completely eliminate bacteria, which may predispose treated teeth to secondary caries. Both propolis and *Aloe vera* extracts can be used as potential natural disinfecting agents, thereby embracing the concept of phytotherapy in minimum intervention dentistry^[164].

SIDE EFFECTS

Although bee-pollen is marketed as a natural health supplement, it has the potential to cause substantial allergic reactions when ingested by patients with pollen allergy. Often, skin tests showing reactivity to common airborne pollens correlates with reactivity to bee pollen. Health care providers should be aware of the potential for reaction, and patients with pollen allergy should be advised of potential risk when consuming the products-it is not known who will have an allergic reaction upon ingestion bee-pollen. Systemic allergic reactions induced by bee-pollen were reported^[165]. Bee-pollen supplement and other products containing grasses or pollens should be avoided, and an epinephrine auto-injector could be prescribed in case of a future reaction^[166].

HONEY

Introduction

Honey is a sweet viscid material made by honey bees (*Apis*

mellifera) using the nectar portion flowers. It varies in its physical and chemical properties. Honey is classified, according to several properties including water content, clarity, colour, aroma, and methods of processing. Honey has been used as a remedy for many illnesses^[167,168]. Honey contains over 200 compounds, consisting mainly of sugars (75% monosaccharides: glucose and fructose; 10%-15% disaccharides: sucrose, maltose, etc.) and water, as well as enzymes, vitamins (Vitamin B₆, riboflavin, niacin, thiamine, etc.), minerals, phenolic compounds (flavonoids, phenolic acids), volatile compounds, and pigments^[169-172]. Raw honey is the honey that does not undergo further processing such as boiling or pasteurization^[167,168]. Medical-grade honey is a purified-type honey that undergoes gamma radiation to help destroy the spores of *Clostridium botulinum*^[167,168].

Anti-oxidant, anti-inflammation and anti-tumor activity

Reactive oxygen species (ROS) and inflammation play an important role in the process of carcinogenesis^[173,174]. The negative side effects of chemotherapeutic treatments can severely impact the quality of life for patients. Therefore, therapies which can prevent progression to malignancy, reduce the required dosage of conventional drugs, or lessen the severity of adverse effects are of considerable benefit^[175].

The antioxidant and anti-inflammatory action of honey has been reported^[176-180] and it was shown that it is related to its phenolic constituent^[169,170,181,182]. These constituents include phenolic acids such as ellagic acid, gallic acid, syringic acid, caffeic acid, chlorogenic acid, *p*-coumaric acid, ferulic acid, and flavonoids^[183,184].

The phenolic content of honey varies between 86 and 1141 mg/kg and is related to some factors including their geographical origin and floral source^[172,183,185-187].

Aberrant proliferation is a defining feature of tumour cells. Cell cycle deregulation underlies uncontrolled cell proliferation leading to tumour formation. Growth arrest at G₀/G₁ and G₂/M phases or apoptosis can be initiated with DNA alterations. Several studies have reported honey treatment of cell lines leading to arrest of cells in the G₀/G₁ phase in bladder (T24, 253 J, RT4, and MBT-2), colon (HCT-15 and HT-29)^[188], and human melanoma (A375)^[189] cell lines. It was worth to note that, the effect was higher in the presence of 6% honey than 12% in the 253J and RT4 cell lines because the apoptotic rate in the presence of 6% honey was higher than 12%, an effect which may be related to the low cell survival rate at a higher concentration of honey^[190].

Tualang honey was shown to exhibit antiproliferative effects on oral squamous cell carcinomas (OSCC) and human osteosarcomas (HOS) cell lines. The 50% inhibitory concentration (IC₅₀) for Tualang honey was 4% for OSCC and 3.5% for HOS cell lines. Because honey is supersaturated with sugar, the authors examined the effects of a mixture of glucose, fructose, and sucrose, and demonstrated that the antiproliferative effect of honey superseded the osmolarity effects of sugars. By testing the antiproliferative effect in the presence of catalase, they demonstrated the cytotoxic effects of hydrogen peroxide and indicated that the antiproliferative effects of honey were due to its phenolic content^[191].

The effect of honey on growth factor signal transduction in cancer cell has been examined. Treatment with gelam honey (40-100 mg/mL) alone and in combination with ginger (honey 10-50 mg/mL plus ginger 3 mg/mL) led to downregulation of Kirsten rat sarcoma viral oncogene homolog (KRAS), extracellular signal-regulated kinase (ERK), and Akt genes in the colorectal cancer cell line HT29^[192]. In dermal fibroblasts, manuka honey, at a concentration of 0.1%, showed a protective effect on 2,2'-azobis(2-amidinopropane)

dihydrochloride (AAPH)-induced stressed cells, by activating 5' AMP-activated protein kinase (AMPK) phosphorylation, and the Nrf2/ARE anti-inflammatory signalling pathway^[193].

In addition, some studies have shown that phenolic compounds can suppress selected growth factors in vitro. Quercetin (100 μM) treatment significantly decreased EGF gene and protein expression in an endometrial cancer cell line (Ishiwaka)^[194]. Treatment with 5–30 μM of caffeic acid phenethyl ester, derived from honeybee propolis, decreased the total abundance and phosphorylation of the epidermal growth factor receptor (EGFR) in MDA-231 breast cancer cells in a dose-dependent manner^[195].

Regulation of apoptosis is critical in cancer pathogenesis, as failure to undergo apoptosis results in an uncontrolled increase in cancerous cells^[196].

Honey has been studied in different cancer cell lines for its ability to induce apoptosis, with various mechanisms of action. The apoptotic effects of a range of Spanish honeys were observed on human peripheral blood promyelocytic leukaemia cells (HL-60)^[197]. The cells were exposed for 24 and 48 h to 2.5% and 5% of three types of honey (heather, rosemary, and polyfloral), as well as an artificial honey composed of sugars (1.8% sucrose, 7.5% maltose, 40.5% fructose, and 33.5% glucose). The results revealed that at a final concentration of 5%, all types of honey showed a significant difference in apoptotic cells when compared to the negative control, with the highest increase being achieved after 48 h of incubation with 5% heather and polyfloral honeys (about a 74% increase of apoptotic cells). The number of apoptotic cells in the honey-treated cells was also higher in comparison to the cells treated with the mixture of sugars. In addition, reactive oxygen species (ROS) production was determined and the authors concluded that the investigated Spanish honeys induced apoptosis in HL-60 cells through a ROS-independent pathway^[197]. An Iranian multifloral honey was found to induce apoptosis on the ACHN renal carcinoma cell lines in a time- and concentration-dependent manner, with the highest number of apoptotic cells being achieved after incubation with 20% honey for 48 h^[198].

In conclusion, honey and its constituents act as anticancer agent through apoptotic mechanism, especially by promoting proapoptotic protein expression and inhibiting the expression of the antiapoptotic protein Bcl-2, as well as by modulating caspase activation, p53 expression, and DNA fragmentation. Some studies found that combining honey with other natural products enhances the apoptotic effects^[175].

Inflammation is a biological response to injury which increases wound healing and plays a role in many pathological processes. Cytokines released from inflammatory cells can trigger angiogenesis or stroma proliferation, while damage caused by reactive oxygen species (ROS) to the surrounding tissues can cause tumour initiating mutations^[199].

Gelam honey extract, as well as quercetin, each used at concentrations of 20, 40, 60, and 80 μg/mL for 24 h, were found to decrease the activation of both NF-κB and MAPK in a dose-dependent manner in the hamster pancreatic cell line HIT-T15^[200]. Another study found that gelam honey and quercetin (used at the same concentrations as previously) also alter JNK signalling in the same cell line, reducing the expression of the proinflammatory cytokines TNF-α, interleukin-6 (IL-6), and interleukin-1β^[201]. However, here was a discrepancy between the pro- and anti-inflammatory properties of honey which may be due to differences in the cell lines and animal models used, as well as the honey type and composition. The phenolic components of honey have anti-inflammatory and antioxidant

properties, which have been proposed as mechanisms for honey's anti-tumour activity. Each variety of honey has varying amounts of these compounds altering their activity^[175].

Angiogenesis is the process of new blood vessel growth, which increases tissue formation by supplying nutrition and oxygen to tissues. This process is important both in wound healing, as well as in the development of malignant tumour^[202]. Cancer cells promote angiogenesis through generation of factors such as bFGF, TNF, and VEGF^[203]. Honey is well known to promote angiogenesis in normal cells, with a varied response at different concentrations. It has been suggested that at low concentrations (0.015-6.2%), honey has proangiogenic effects, which disappears at higher concentrations (> 12.5%). Honey has been shown to decrease VEGF formation at high concentrations^[124]. In a study using air pouch model of inflammation, honey has been shown to inhibit the angiogenic agents PGE2 and VEGF^[204]. Another study using 7,12-dimethylbenz(a)anthracene-induced breast cancer rats, tualang honey, at concentrations as low as 0.2 g/kg, significantly decreased the cancer growth, increased the number of apoptotic cells, and decreased VEGF levels and the vasculature around the tumour^[205].

Metastasis is the most destructive feature of cancer and consists of highly complex mechanisms^[206] involving different molecules^[207]. In *in vivo* study performed using wildflower honey from Croatia before and after tumour cell inoculation of CBA mice and Y59 rats, honey was found to have a significant anti-metastatic effect when used before tumour inoculation^[208]. The mice were injected intravenously with spontaneous mammary carcinoma (MCA) cells and methylcholanthrene-induced fibrosarcoma (FS) cells, while the rats were injected with transplantable anaplastic colon adenocarcinoma (ACa) cells. The mice received an oral dose of 2 g/kg, while the dose for the rats was 1 g/kg of wildflower honey from Croatia, for 10 days before and after treatment. Interestingly, when honey was administered two days after tumour cell inoculation, there was no effect on the formation of tumour nodules in mice, while in rats more enhanced tumour growth was observed. The authors associated this effect with activation of the immune system (specifically macrophages) by honey when used before tumour inoculation (preventatively)^[208].

Wound healing activity

Wound healing is a complex process involving several stages with many internal and external factors playing different important roles. Healing of wounds can be hindered in special cases and successful management becomes a serious challenge to the practitioner. Many natural and synthetic products have been tried in both human and animals to facilitate the process of healing especially in unusual wounds^[209].

The use of honey as a wound care product has been recognized. Various mechanisms have made honey superior to many other available medically-approved wound care products. Honey has a hygroscopic effect by attracting and holding excessive fluid from the surrounding environment and thus reduces inflammatory oedema and exudation associated with the healing process. Reduction in inflammatory oedema and exudation also may decrease pain^[167,168]. The high sugar content in honey provides a source of energy to both the viable cells as well as wound invading bacteria^[210]. Wound invading bacteria preferably utilizes high glucose content, which in turn produces lactic acids rather than malodorous products thus reducing unpleasant odours associated with many types of wounds. Honey's low water content creates high osmolarity conditions in contaminated wounds. As a result, nutrients will be dissolved within

the lymph drawn from the wound area for tissue regeneration.

Recently, honey is considered an efficient natural antibacterial in wounds infected with multidrug resistant bacteria such as *Staphylococcus*, *Streptococcus*, *Pseudomonas* and *E. coli*^[210].

The exact mechanism of action of honey as an effective antibacterial agent has been demonstrated. Suggested mechanisms are many and include low water content, high acidity, high osmolality, presence of natural hydrogen peroxide that is produced by the action of glucose oxidase in honey, and radical scavenging properties due to phenolic compounds^[210-216]. Hydrogen peroxide produced in honey also plays a protective role that prevents tissues from damage^[216-218].

Sidr honey has been utilized as an effective treatment for infected wounds. Alzubier and Okechukwu have investigated the *in vitro* antibacterial activity of Sidr honey. The potent bactericidal activity of this honey against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms was evidenced^[219]. The study concluded that both Manuka and Sidr honeys have superior antimicrobial properties that surpass the activity of commonly used antibiotics^[220]. More interestingly, in addition to its antibacterial and anti-inflammatory activities, this honey has a variety of other medicinal effects such as anti-parasitic^[221], antifungal^[210], antiviral^[222] and anticarcinogenic^[223,224] activities.

Sidr honey obtained from Sidr tree has been known also to cure liver diseases, chronic rhinosinusitis and gastrointestinal ulcers in humans^[220]. A recent research utilized Sidr honey in rat model showed that honey inhibited histamine, carrageenan-induced paw oedema, acetic acid-induced writhing, formalin induced writhing, and significantly reduced yeast induced pyrexia with no observed toxic side effects^[219]. Furthermore, Sidr honey has expressed numerous medicinal effects including antibacterial, anti-inflammatory, antipyretic and analgesic activities^[219,220].

Honey with *Aloe vera*

Tomasin R. and Gomes-Marcondes M.C. reported that oral administration of *Aloe vera* and honey reduces Walker tumour growth by decreasing cell proliferation and increasing apoptosis in tumour tissue^[225]. This study verified the influence of *Aloe vera* and honey on tumour growth and in the apoptosis process by assessing tumour size, the cell proliferation rate (Ki67-LI) and Bax/Bcl-2 expression at 7, 14 and 20 days after Walker 256 carcinoma implant in Wistar rats divided into two groups: tumour-bearing rats group that received a gavage with a 670 mL/kg dose of *Aloe vera* and honey solution daily, and tumour-bearing rats which received only saline solution. The Bax/Bcl-2 ratio increased in tumours from the treated group at all tested time points. These data suggested that *Aloe vera* and honey can modulate tumour growth by reducing cell proliferation and increasing apoptosis susceptibility^[225]. Furthermore, *Aloe vera* and honey solution decreased host wasting and also increased oxidative stress in tumor cells, when administered therapeutically, by differentially modulating antioxidant and proteolysis enzymes in the host and tumor tissues. The mechanisms responsible for these effects might include the deleterious actions of various *Aloe vera* and honey compounds (aloin, aloe-emodin, acemannan, and flavonoids) on tumor cells, which might result in indirect effects on the host tissues. These mechanisms may also include immune system modulation as well as altering the chronic proinflammatory status of cancer-induced cachexia. Several compounds in *Aloe vera* and honey synergized to generate the observed effects in this model^[226].

A study investigating oral administration of honey combined with *Aloe vera* found an increase in apoptosis in Wistar rats implanted subcutaneously with a Walker 256 carcinoma cell suspension^[225]. The

rats received daily dose of 670 mL/kg solution containing honey and *Aloe vera*. The tumour cells were examined at 7, 14 and 20 days. The study that the *Aloe vera* and honey mixture increased the expression of the proapoptotic protein Bax, especially on day 20, while inhibiting expression of the antiapoptotic protein Bcl-2, especially in the early stages of the tumour development (day 7 and day 14). This study showed that honey and *Aloe vera* can modulate tumour growth by increasing the susceptibility to apoptosis^[225].

RESPONSE OF CHRONIC FATIGUE SUBJECTS TO THE INGESTION OF ALOE VERA JUICE WITH OR WITHOUT BEE-PRODUCTS (PROPOLIS AND POLLEN), AND CASE REPORTS

The questionnaire included 10 points regarding the health conditions and the scoring was recorded from top six conditions in Table 1 and 2. Table 1 and 2 demonstrated the personal experiences on administration of *Aloe vera* juice with or without bee-products supplement under the agreement of the principal of the Helsinki declaration. Specially, the results in Table 2 having an available recovery ratio showed high responses in plural answer. The results are shown in Figure 1. Ingestion of *Aloe vera* juice with bee-product supplement provided the noteworthy information for putative prophylaxes to improve chronic fatigue and languid syndrome. Furthermore, case reports on obesity and ulcerative colitis: daily ingestion of *Aloe vera* juice and bee-products, were demonstrated in Table 3.

FUTURE PROSPECTIVES

Propolis

Scientific opinion on the substantiation of health claims related to propolis and flavonoids in propolis pursuant to Article 13(1) of regulation (EC) No 1924/2006, addressed as following: The references provided reported on differences in biological activity between propolis preparations from different sources. Levels of what are assumed to be biologically active constituents in some propolis preparations are low or undetectable in other propolis preparations. Further, the papers provided for the scientific substantiation of the claims reported on a wide range of different propolis preparations, extracts and isolated components, and it is not clear for which type of propolis preparation/constituent the claims are made. On the basis of the data presented, European Food Safety Authority (EFSA) Panel concluded that a cause and effect relationship cannot be established between the consumption of propolis or of flavonoids in propolis and the claimed effects considered in this opinion such as respiratory health, antibacterial and antifungal activities, and so on^[227]. The regulation 1924/2006 is put into practise and an evaluation from the EFSA is still in progress.

Propolis is one of the few natural products that have maintained its popularity over a long period of time. Propolis contains broad *in vitro* and *in vivo* biological properties, which provide new possibilities for incorporation of propolis components in cosmetic products, foodstuffs and medicines. Despite the *in vitro* and *in vivo* assays, which provide new valuable information on propolis biological properties and mechanisms of action, it will be necessary to analyse the effectiveness of propolis clinically, to complement the basic research available, and to evaluate the potential of propolis in human health promotion^[228]. On recent report, propolis was clinically applied for oral mucositis in Memorial Sloan Kettering Cancer Center^[229].

Pollen

The German Federal of Health had officially recognized bee-pollen as a medicine^[230]. As Nechaeva N., reported in “change of functional and sports medicine after intake of bee-products”, the adaptogenic properties of pollen, which are based on increasing the resistance to harmful physical, chemical, and biological factors, were indicated: it is both (i) increasing the physical fitness of the organism in excessive physical burden, affecting the central nervous system by improving brain functions, such as memory, learning, comprehending, thinking and ability to concentration, and (ii) increasing the immune system strengths against infection en route boosting the immunological system^[231]. Some papers related to nutritional and therapeutic claims supported by scientific based evidence have been published on bee-pollen. Once bee-pollen was defined in legislation as food, the nutritional value of this product became important. The quality of bee-pollen products originally starts to be influenced by bees at pollen collection. The technologies harvesting mono-floral pollen and the bee-pollen storage by beekeepers are necessary to obtain a more standardized bee-pollen. Future research on bee-pollen needs to develop legislation in order to have “Harmonized standard quality control” and summarized the knowledge on bee-pollen in regard to nutrition and possible health enhancing and therapeutic applications for a future possible market. Monofloral or standard bee-pollen should be determined and identified, and in a final step pollen types with optional pharmacological properties can be tested in human therapy and clinical studies^[232].

European parliament and council (2007) regulation (EU) No 1924/2006 of the European Parliament and of the council of 20 December 2006 on nutrition and health claims made on food. Official J.of the EU.L 404: L 12-3-L12/17. Two health claims according to the EU regulation 1924/2006; (i) Physical performance and fitness: Long-term ingestion of pollen and special pollen preparations can improve the physical performance and fitness of sportsmen and elderly people. (ii) Gut, digestion and liver health: Pollen intake can improve gut, gastroenterological and health^[233].

Review article, Nature treasure: *Aloe vera* and Bee-products, presents information available for bee-products as functional foods. The demonstrated efficacies of *Aloe vera* juice ingestion with bee products (bee-propolis and bee-pollen) supplement shown in Table 2 compared with to the single respondent in Table 1, may promise greater possibility for promoting muscle performance and blood circulation, and enhancing quality of life in menopausal women and benign prostatic hyperplasia in men. The results of questionnaire: Response of chronic fatigue and languid subjects to the ingestion of *Aloe vera* juice with bee-product, provided noteworthy improvement as one of natural treasure. Furthermore, case reports in Table 3 demonstrated that daily ingestion of AVJ with bee products potently improved metabolic syndrome and remitted inflammation around the under-rectum in ulcerative colitis. Daily ingestion of AVJ with bee-products may complement the basic quality of life available.

Questionnaire assessment of volunteer 507 subjects of male: 66, female: 423, unknown, 18; ranging from 20 to 70 years old; recovery ratio: 13.8% in single respondent from the total 3681, was carried out during September 1 to November 27, 2014. One hundred ml of International Aloe Science Council (IASC)-certificated *Aloe vera* juice (Forever Living Product, Japan) was orally ingested once a day for three months. Questionnaire evaluation was based on the following:

Scheme: 1. No change, 2. Slight better, 3. Very much better, 4. Slight worse, 5. Very worse. In order to fairly evaluate the juice, only response to question No.3 was adopted as positive in each health

condition. There was no adverse effect throughout three months of the trial period.

Questionnaire assessment of volunteer: 2525 (propolis), 2622 (pollen), 2679 (bee-products) subjects; age-range from 20 to 70 years old; recovery ratio: 68.6% (propolis); 71.2% (pollen); 72.8% (bee-products) in plural respondent in the total 3681 (male: 315, female 3286, unknown 80), was carried out during September 27, 2014 to November 27, 2014. Two hundred ml of IASC-certified *Aloe vera* juice with bee-pollen and/or propolis (Forever Living Product, Japan) was orally ingested once a day for three months. Questionnaire evaluation was based on the following Scheme: 1. No changed, 2. Slight better, 3. Very much better, 4. Slight worth, 5. Very worse. In order to fairly evaluate the juice, only response to question No.3 was adopted as positive in each health condition. There was no adverse effect throughout three months of trial period.

SUMMARY

The efficacies of AVJ ingestion with bee-products supplement were demonstrated to the subjects of health troubles by questionnaire assessment and improved health conditioning to respondents shown in Figure 1. A possible contribution of bee-products with AVJ ingestion to health and QOL was estimated as a beneficial nutraceutical.

ACKNOWLEDGEMENTS

The authors express their deep gratitude to Forever Living Product Japan for supplying *Aloe vera* juice and bee products supplements, and totaling of questionnaire.

REFERENCES

1. Kwon TD, Lee MW, Kim KH. The effect of exercise training and water extract from propolis intake on the antioxidant enzymes activity of skeletal muscle and liver in rat. *J Exer Nutr Biochem* 2014; **18** (1): 9-17. [DOI: 10.5717/jenb.2014.18.1.9]
2. Bradbear N. Bees and their role in forest livelihoods: a guide to the services provided by bees and the sustainable harvesting, processing and marketing of their products. *Food and Agriculture Organization of the United Nations* 2009- Business & Economics pp 120-121.
3. Linskens HF, Jorde W. Pollen as food and medicine: A review. *Econ. Bot.* 1997; **51**: 78-86. [DOI: 10.1007/BF02910407]
4. Campos MGR, Frigerio C, Lopes J, Bogdanov S. What is the future of Bee-Pollen? *J. Apipro. Apimed. Sci.* 2010; **2**: 131-144. [DOI: 10.3896/IBRA.4.02.4.01]
5. Campos MGR, Bogdanov S, Almeida-Muradian LB, Szczesna T, Mancebo Y, Frigerio C, Ferreira F. Pollen composition and standardisation of analytical methods. *J. Apic. Res.* 2008; **47**: 154-161. [DOI: 10.1080/00218839.2008.11101443]
6. Rzepecka-Stojko A, Stojko J, Kurek-Górecka A, Górecki M, Kabała-Dzik A, Kubina R, Moździerz A, Buszman E. Polyphenols from Bee Pollen: Structure, Absorption, Metabolism and Biological Activity. *Molecules* 2015; **20**: 21732-21749. [PMID: 26690100]; [DOI: 10.3390/molecules201219800]
7. Nogueira C, Iglesias A, Feás X, Estevinho LM. Commercial bee-pollen with different geographical origins: A comprehensive approach. *Int. J. Mol. Sci.* 2012; **13**: 11173-11187. [PMID: 23109845]; [DOI: 10.3390/ijms130911173]
8. Rzepecka-Stojko A, Maciejewska-Paszek I, Stec M, Kurzeja E, Kęska A, Pawłowska-Góral K. The influence of extraction method on obtaining polyphenolic compounds from bee pollen. *Farm Prz Naukowy* 2010; **1**: 38-41.
9. Carpes ST, Mourão GB, Alencar SM, Masson ML. Chemical composition and free radical scavenging activity of *Apis mellifera* bee-pollen from Southern Brazil. *Braz. J. Food Technol.* 2009; **12**: 220-229. [DOI: 10.4260/BJFT2009800900016]
10. Almaraz-Abarca N, da Graça Campos M, Ávila-Reyes JA, Naranjo-Jiménez N, Carrol HJ, González-Valdez LS. Antioxidant activity of polyphenolic extract of monofloral honeybee-collected pollen from mesquite (*Prosopis juliflora*, Leguminosae). *J. Food. Compos. Anal.* 2007; **20**: 119-124. [DOI: 10.1016/j.jfca.2006.08.001]
11. Almeida-Muradian LB, Pamplona LC, Coimbra S, Barth OM. Chemical composition and botanical evaluation of dried bee-pollen pellets. *J. Food Compos. Anal.* 2005; **18**: 105-111. [DOI: 10.1016/j.jfca.2003.10.008]
12. Feás X, Vázquez-Tato MP, Estevinho L, Seijas JA, Iglesias A. Organic bee pollen: botanical origin, nutritional value, bioactive compounds, antioxidant activity and microbiological quality. *Molecules*. 2012; **17**(7): 8359-8377. [DOI: 10.3390/molecules17078359]
13. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic. Biol. Med.* 1996; **20**: 933-956. [PMID: 8743980]
14. Almaraz-Abarca N, da Graça Campos M, Ávila-Reyes JA, Naranjo-Jiménez N, Herrera-Corral J, González-Valdez, LS. Variability of antioxidant activity among honey bee-collected pollen of different botanical origin. *Interciencia-Caracas* 2004; **29**: 574-578.
15. Kędzia B. Chemical composition and adaptogenic activity of honeybee-collected pollen. Part one. Chemical composition. *Postep. Fitoter.* 2008; **1**: 47-58.
16. Šarić A, Balog T, Sobočanec S, Kušić B, Šverko V, Rusak G, Likić S, Bubalo D, Pinto B, Reali D, Marotti T. Antioxidant effects of flavonoid from Croatian *Cystus incanus* L. rich bee pollen. *Food Chem. Toxicol.* 2009; **47**: 547-554. [PMID: 19124059]; [DOI: 10.1016/j.fct.2008.12.007]
17. Serra Bonvehi J, Soliva Torrentó M, Centelles Lorente E. Evaluation of polyphenolic compounds in honeybee-collected pollen produced in Spain. *J. Agric. Food Chem.* 2001; **49**: 1848-1853. [PMID: 11308335]
18. Leja M, Mareczek A, Wyzgolik G, Klepacz-Baniak J, Czekońska K. Antioxidative properties of bee-pollen in selected plant species. *Food Chem.* 2007; **100**: 237-240. [DOI: 10.1016/j.foodchem.2005.09.047]
19. Gulcin I. Antioxidant activity of food constituents: An overview. *Arch. Toxicol.* 2012; **86**: 345-391. [PMID: 22102161]; [DOI: 10.1007/s00204-011-0774-2]
20. Graikou K, Kapeta S, Aligiannis N, Sotiroidis G, Chondrogiani N, Gonos E, Chinou I. Chemical analysis of Greek pollen - Antioxidant, antimicrobial, and protease activation properties. *Chem. Cent. J.* 2011; **5**. [DOI: 10.1186/1752-153X-5-33]
21. Arráez-Román D, Zurek G, Bässmann C, Almaraz-Abarca N, Quirantes R, Segura-Carretero A, Fernández-Gutiérrez A. Identification of phenolic compounds from pollen extracts using capillary electrophoresis-electrospray time-of-flight mass spectrometry. *Anal. Bioanal. Chem.* 2007; **389**: 1909-1917. [PMID: 17899027]; [DOI: 10.1007/s00216-007-1611-6]
22. Čeksteryte V, Kazlauskas S. Composition of flavonoids in Lithuanian honey and bee bread. *Biologija* 2006; **2**: 28-33.
23. Silva TMS, Camara CA, da Silva Lins AC, Barbosa-Filho JM, da Silva EMS, Freitas BM, dos Santos FDAR. Chemical composition and free radical scavenging activity of pollen loads from stingless bee *Melipona subnitida* Ducke. *J. Food Compos. Anal.* 2006; **19**: 507-511. [DOI: 10.1016/j.jfca.2005.12.011]
24. Martins MCT, Morgano MA, Vicente E, Baggio SR, Rodriguez-Amaya DB. Physicochemical composition of bee-pollen from eleven Brazilian states. *J. Apic. Sci.* 2011; **55**: 107-116.
25. Szczesna T. Study on the sugar composition of honeybee-collected pollen. *J. Apic. Sci.* 2007; **51**: 15-22.

26. Roulston TH, Cane JH. Pollen nutritional content and digestibility for animals. *Plant Syst. Evol.* 2000; **222**: 187-209. [DOI: 10.1007/BF00984102]
27. Stanley RG, Linskens HF. Pollen. Biology - Biochemistry - Management. Springer-Verlag Berlin, Heidelberg. 1974.
28. Serra Bonvehi J, Gonell Galindo J, Gomez Pajuelo A. Estudio de la composicion y características fisico-químicas del polen de abejas. *Alimentaria* 1986; 63-67.
29. Simopoulos A. Omega-3 fatty acids in health and disease and in growth and development. *Am. J. Clin. Nutr.* 1991; **54**: 438-463. [PMID: 1908631]
30. Herbert EW, Jr, Miller-Ihli NJ. Seasonal variation of seven minerals in honey bee collected pollen. *Am. Bee J.* 1987; 367-369.
31. Somerville DC, Nicol HI. Mineral content of honeybee-collected pollen from southern New South Wales. *Aust. J. Exp. Agric.* 2002; **42**: 1131-1136. [DOI: 10.1071/EAD1086]
32. Bell RR, Thornber EJ, Seet JLL, Groves MT, Ho NP, Bell DT. Composition and protein quality of honey-bee-collected pollen of *Eucalyptus marginata* and *Eucalyptus calophylla*. *J. Nutr.* 1983; **113**: 2479-2484. [PMID: 6655512]
33. Percie Du Sert P. Les pollens apicoles. *Phytotherapie* 2009; **7**: 75-82.
34. Shkenderov S, Ivanov T. Pcelni Produkti, The Bee Products (in Bulgarian). *Zemizdat (Abstract in Honey bibliography)*: 1983; 1-238.
35. Bogdanov S. Pollen: Production, Nutrition and Health: A review. Bee Products Science, www.bee-hexagon.net, April 2015 (p 1-35).
36. Xue X, Zhao J, Chen L, Zhou J, Yue B, Li Y, Wu L, Liu F. Analysis of coenzyme Q₁₀ in bee-pollen using online cleanup by accelerated solvent extraction and high performance liquid chromatography. *Food Chem.* 2012; **133**: 573-578. [DOI: 10.1016/j.foodchem.2011.12.085]
37. Marcucci MC, Ferreres F, Garca-Viguera C, Bankova VS, De Castro SL, Dantas AP, Valente PHM, Paulino N. Phenolic compounds from Brazilian propolis with pharmacological activities. *J. Ethnopharmacol.* 2001; **74**: 105-112. [PMID: 11167028]
38. Walgrave, SE, Warshaw EM, Glesne LA. Allergic contact activity of honey and propolis from *Apis mellifera* and *Tetragonisca angustula* against 2-Castro SL. *J. Appl. Microbiol.* 2005; **95**: 913-920.
39. Watanabe MA, Amarante MK, Conti BJ, Sforzin JM. Cytotoxic constituents of propolis inducing anticancer effects: a review. *J. Pharm. Pharmacol.* 2011; **63**, 1378-1386. [PMID: 21988419]; [DOI: 10.1111/j.2042-7158.2011.01331]
40. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem. Toxicol.* 1998; **36**: 347-63. [PMID: 9651052]
41. Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. *Fitoterapia.* 2002; **73**: S1-6. [PMID: 12495704]
42. Miorin PL, Levy Junior NC, Custodio AR, Bretz WA, Marcucci MC. Antibacterial activity of honey and propolis from *Apis mellifera* and *Tetragonisca angustula* against *Staphylococcus aureus*. *J. Appl. Microbiol.* 2003; **98**: 913-920. [PMID: 14633019]
43. Gómez-Caravaca AM, Gómez-Romero M, Arráez-Román D, Segura-Carretero A, Fernández-Gutiérrez A. Advances in the analysis of phenolic compounds in products derived from bees. *J. Pharm. Biomed. Anal.* 2006; **41**: 1220-1234. [DOI: 10.1016/j.jpba.2006.03.002]
44. Aga H, Shibuya T, Sugimoto T, Kurimoto M, Nakajima SH. Isolation and identification of antimicrobial compounds in Brazilian propolis. *Biosci. Biotechnol. Biochem.* 1994; **58**: 945-946. [DOI: 10.1271/bbb.58.945]
45. Russo A, Longo R, Vanella A. Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. *Fitoterapia* 2002; **73**: 21-29. [PMID: 12495706]
46. Draganova-Filipova MN, Georgieva MG, Peycheva EN, Miloshev GA, Sarafian VS, Peychev LP. Effects of propolis and CAPE on proliferation and apoptosis of McCoy-Plovidiv cell line. *Folia Medica* 2008; **50**: 53-59. [PMID: 18543789]
47. Liao HF, Chen YY, Liu JJ, Hsu ML, Shieh HJ, Liao HJ, Shieh CJ, Shiao MS, Chen YJ. Inhibitory effect of caffeic acid phenethyl ester on angiogenesis, tumor invasion, and metastasis. *J. Agric. Food Chem.* 2003; **51**: 7907-7912. [DOI: 10.1021/jf034729d]
48. Chen YJ, Liao HF, Tsai TH, Wang SY, Ming-Shi 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**: 1252-1261. [PMID: 16253780]; [DOI: 10.1016/j.ijrobp.2005.08.001]
49. White JW. "Composition of honey," in Honey: A Comprehensive Survey, E. Crane, Ed., pp. 157-206, Bee Research Association and Chalfont St Peter, London, UK, 1975.
50. El Denshary ES, Al-Gahazali MA, Mannaa FA, Salem HA, Hassan NS, Abdel-Wahhab MA. Dietary honey and ginseng protect against carbon tetrachloride-induced hepatonephrotoxicity in rats. *Exp. Toxicol. Pathol.* 2012; **64**: 753-760. [PMID: 21330121]; [DOI: 10.1016/j.etp.2011.01.012]
51. Khalil MI, Sulaiman SA, Boukraa L. Antioxidant properties of honey and its role in preventing health disorder. *Open Nutraceut. J.* 2010; **3**: 6-16. [DOI: 10.2174/18763960010030100006]
52. Cortés ME, Vigil P, Montenegro G. The medicinal value of honey: a review on its benefits to human health, with a special focus on its effects on glycemic regulation. *Cien. Inv. Agr.* 2011; **38**: 303-317. [DOI: 10.4067/S0718-16202011000200015]
53. Alvarez-Suarez JM, Tulipani S, Romandini S, Bertoli E, Battino M. Contribution of honey in nutrition and human health: a review. *Med. J. Nutrition Metab.* 2010; **3**: 15-23. [DOI: 10.3233/s12349-09-0051-6]
54. Tomasin R, de Andrade RS, Gomes-Marcondes MC. Oral administration of *Aloe vera* (L.) Burm. F. and honey improves the host body composition and modulates proteolysis through reduction of tumor progression and oxidative stress in rats. *J. Med. Food* 2015; **18**: 1128-1135. [PMID: 25856497]; [DOI: 10.1089/jmf.2014.0129]
55. Yagi A. Putative prophylaxes of *Aloe vera* latex and inner gel as immunomodulator. *J. Gastroenterol. Hepatol. Res.* 2015; **4**: 1585-1598 [DOI: 10.17554/j.issn.2224-3992.2015.04.506]
56. Yagi A, Ataka S. Putative prophylaxes updated of placenta extract and *Aloe vera* as biogenic stimulants. *J. Gastroenterol. Hepatol. Res.* 2014; **3**: 1367-1387. [DOI: 10.6051/j.issn.2224-3992.2014.03.443]
57. Yagi A. *Aloe vera* high molecular weight fractions as carbohydrate based immune adjuvants. *J. Gastroenterol. Hepatol. Res.* 2013; **2**: 568-570. [DOI: 10.6051/j.issn.2224-3992.2013.02.114]
58. Yagi A. Therapeutic efficacy of *Aloe vera* high molecular fractions for treatment of hepatic fibrosis, type 2 diabetes, bed sores and lichen planus. *J. Gastroenterol. Hepatol. Res.* 2013; **2**: 672-679. [DOI: 10.6051/j.issn.2224-3992.2013.02.235]
59. Yagi A. Putative prophylaxes of *Aloe vera* for age-related diseases. *J. Gastroenterol. Hepatol. Res.* 2015; **4**: 1407-1224. [DOI: 10.6051/j.issn.2224-3992.2015.04.416]
60. Yagi A. Possible efficacy of *Aloe vera* gel metabolites in long-term ingestion to insulin sensitivity. *J. Gastroenterol. Hepatol. Res.* 2014; **3**(3): 996-1005 [DOI: 10.6051/j.issn.2224-3992.2014.03.385]
61. Yagi A, Yu BP. Immune modulation of *Aloe vera*: acemannan and gut microbiota modulator. *J. Gastroenterol. Hepatol. Res.* 2015; **4**: 1707-1721. [DOI: 10.17554/j.issn.2224-3992.2015.04.525]
62. Yagi A, Ataka S. Putative prophylaxes of *Aloe vera* juice with L-arginine to chronic fatigue syndrome. *J. Gastroenterol. Hepatol. Res.* 2016; **5**: 1950-1956. [DOI: 10.17554/j.issn.2224-3992.2016.5.603]
63. Khalil MI, Tanvir EM, Rizwana A, Sulaiman SA, Gan SH.

- Cardioprotective Effects of Tualang Honey: Amelioration of Cholesterol and Cardiac Enzymes Levels. *Bio. Med. Res. Int.* 2015; **2015**: 1-8.[DOI: 10.1155/2015/286051]
64. Moniruzzaman M, Khalil MI, Sulaiman SA, Gan SH. Physicochemical and antioxidant properties of Malaysian honeys produced by *Apis cerana*, *Apis dorsata* and *Apis mellifera*. *BMC Complement. Altern. Med.* 2013; **13**: 43. [DOI: 10.1186/1472-6882-13-43]
 65. Molan P. The antibacterial activity of honey. *Bee World*, 1992; **73**: 59-76. [DOI: 10.1080/0005772x.1992.11099109]
 66. Kubota Y, Umegaki K, Kobayashi K, Tanaka N, Kagota S, Nakamura K, Kunitomo M, Shinozuka K. Anti-hypertensive effects of Brazilian propolis in spontaneously hypertensive rats. *Clin. Exp. Pharmacol. Physiol.* 2004; **31**: S29-S30. [PMID: 15649281]; [DOI: 10.1111/j.1440-1681.2014.04113.x]
 67. Morello S, Vellecco V, Alfieri A, Mascolo N, Cicala C. Vasorelaxant effect of the flavonoid galangin on isolated rat thoracic aorta. *Life Sci.* 2006; **78**: 825-830. [PMID: 16169019]; [DOI: 10.1016/j.lfs.2005.05.072]
 68. Teles F, da Silva TM, da Cruz Júnior FP, Honorato VH, de Oliveira Costa H, Barbosa APF, de Oliveira SG, Porfirio Z, Libório AB, Borges RL, Fanelli C. Brazilian red propolis attenuates hypertension and renal damage in 5/6 renal ablation model. *PLOS ONE* 2015; **10**: e0116535. [PMID: 25607548]; [DOI: 10.1371/journal.pone.0116535]
 69. Mishima S, Yoshida C, Akino S, Sakamoto T. Anti-hypertensive effects of Brazilian propolis: Identification of caffeoylquinic acids as constituents involved in the hypotension in spontaneously hypertensive rats. *Biol. Pharm. Bull.* 2005; **28**: 1909-1914. [PMID: 16204944]; [DOI: 10.1248/bpb.28.1909]
 70. Cicala C, Morello S, Lorio C, Capasso R, Borrelli F, Mascolo N. Vascular effects of caffeic acid phenethyl ester on isolated rat thoracic aorta. *Life Sci.* 2003; **73**: 73-80. [PMID: 12726885]; [DOI: 10.1016/s0024-3205(03)00235-2]
 71. Maruyama H, Sumitou Y, Sakamoto T, Araki Y, Hara H. Anti-hypertensive effects of flavonoids isolated from Brazilian green propolis in spontaneously hypertensive rats. *Biol Pharm. Bull.* 2009; **32**: 1244-1250. [PMID: 19571393]; [DOI: 10.1248/bpb.32.1244]
 72. Briones AM, Touyz RM. Oxidative stress and hypertension: current concepts. *Curr. Hypertens. Rep.* 2010; **12**: 135-142. [PMID: 20424957]; [DOI: 10.1007/s11906-610-0100-z]
 73. Fanelli C, Zatz R. Linking oxidative stress, the renin-angiotensin system, and hypertension. *Hypertens.* 2011; **57**: 373-374. [DOI: 10.1161/HYPERTENSIONAHA.110.167775]
 74. Jaimes EA, Galceran JM, Raij L. Angiotensin II induces superoxide anion production by mesangial cells. *Kidney Int.* 1998; **54**: 775-784. [PMID: 9734602]; [DOI: 10.1046/j.1523-1755.1998.00068x]
 75. Vaziri ND, Dicus M, Ho ND, Boroujerdi-Rad L, Sindhu RK. Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. *Kidney Int.* 2003; **63**: 179-185. [PMID: 12472781]; [DOI: 10.1046/j.1523-1755.2003.00702x]
 76. Lifterovr, Fomin W, Shishkina L, Agafonova W, Soldatov EGE, Marhovskaya I, Pushkareva S. Experience with the use of bee bread for the treatment of dyslipidemia of patients with high or intermediate risk for heart disease having arterial hypertension. Apitherapy today (in Russian), *Ribnoe*: 2009; 54-55.
 77. Koslik S, Takac M. Beeinflussung der Hypertriglyzeridämie und Urikämie von dauerlysebehandelten Patienten durch Pollen. *Das Deutsche Gesundheitswesen.* 1979; **34** (38): 1850-1853.
 78. Georgijewa E, Wassileff W. Pollen against Anemia, 29 Apimondia Kongress in Budapest. 1993; pp 106.
 79. Kassyanenko V, Komisarenko I, Dubtsova E. Influence of honey, pollen and bee bread on serum cholesterolin of patients with pathological lipid metabolism (Russian), Beekeeping, apitherapy and life quality, International Industrial Academy, Moscow, 2010; **20**: 81-82.
 80. Polanski M, Okon K, Przybylo R, Frask W. Cardioprotective properties of hydrophilic pollen extract. *Pol. J. Pathol.* 1998; **49**: 109-112. [PMID: 9798415]
 81. Georgiev DB, Melka M, Huber JC, Goudev AR, Manassiey N. Effects of an herbal medication containing bee products on menopausal symptoms and cardiovascular risk markers: results of a pilot open-uncontrolled trial. *Med. Gen. Med.* 2004; **6**: 46.[PMID: 15775873]
 82. Dutkiewicz S. Guidelines for the diagnosis and qualification for treatment of benign prostatic hyperplasia. *Ter. Lek.* 1992; **20**: 42: 29.
 83. Hald T. Review of current treatment of benign prostatic hyperplasia. *Eur. Urol.* 1994; **25** (Suppl I), 15.[PMID: 7507051]
 84. Becker H, Ebeling L. Konservative therapie der benignen prostatahyperplasie (BPH) mit cernilton. *N. Urologe [B]*, 1988; **28**: 301.
 85. Vahlensieck W, Rutishauser G. (eds.): Benign Prostate Diseases. G. Thieme-Verlag, Stuttgart New York 1992.
 86. 86. Loshen G, Ebeling L. Hemmung der Arachidonsaure-Kaskade durch einen Extrakt aus Roggenpollen. *Arzneimittelforschung.* 1991; **41**: 162.
 87. Duikiewicz S. Usefulness of Cernilton in the treatment of benign prostatic hyperplasia. *Int. Urol. Nephrol.* 1996; **28**: 49-53. [PMID: 8738619]
 88. Buck AC, Cox R, Rees RWM, Ebeling L, John A. Treatment of Outflow Tract Obstruction due to Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton A Double-blind, Placebo-controlled Study. *Br. J. Urol.* 1990; **66**: 398-404. [PMID: 1699628]
 89. Wilson, JD. The pathogenesis of benign prostatic hyperplasia. *Am. J. Med.* 1980; **68**: 745-756. [PMID: 6155068]
 90. Habib FK, Tesdale AJ, Chisholm GD, Busuttill A. Androgen metabolism in the epithelial and stromal components of the human hyperplastic prostate. *J. Endocrinol.*, 1981; **9**: 23-32. [DOI: 10.1677/joe.0.0910023]
 91. Fowler FJ, Wennberg JE, Timothy RP, Barry MJ, Mulley AG Jr, Hanley D. Symptom status and quality of life following prostatectomy. *J. Am. Med. Assoc.* 1988; **259**: 3018-3022. [PMID: 2452905]; [DOI: 10.1001/jama1988.037202000400300]
 92. Macdonald R, Ishani A, Rutks I, Wilt TJ. A systematic review of Cernilton for the treatment of benign prostatic hyperplasia. *BJU Int.* 1999; **85**,836-841. [PMID: 10792162]; [DOI: 10.1046/j.1464-410x.2000.00365x]
 93. Ito R, Ishii M, Yamashita S, Noguchi K, Ohkubo Y, Tsushima Y, Sato S, Akamatsu H. Antiprostatic hypertrophic action of Cernilton pollen-extract. *Pharmacometrics* 1986; **31**: 1-11.
 94. Kimura M, Kimura I, Nakase K, Sonobe T, Mori E. Micturition activity of pollen extract: contractile effects on bladder and inhibitory effects on urethral smooth muscle of mouse and pig. *Planta Med* 1986; **2**: 148-151. [PMID: 3725935]
 95. Nakase S, Takenaka K, Hamanaka T, Kimura M. Effects of Cernilton pollen-extract on the urethral smooth muscle and diaphragmatic neuromuscular specimen. *Folio. Pharmacol. Japan* 1988; **91**: 385-392.
 96. Wagenlehner FW, Schneider H, Ludwig M, Schnitker J, Brähler E, Weidner W. A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: A multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. *Eur Urol.* 2009; **56**: 544-551. [PMID: 19524353]; [DOI: 10.1016/j.eururo.2009.05.046]
 97. Bjerklund Johansen TE, Gruneberg RN, Guibert J, Hofstellen A, Lobel B, Naber KG, Polou Redorta J, van Cangh PJ. The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. *Eur. Urol.* 1998; **34**: 457-466. [PMID: 9831786]
 98. Rugendorff EW, Weidner W, Ebeling L, Buck AC. Results of Treatment with Pollen Extract (Cernilton® N) in Chronic

- Prostatitis and Prostatodynia. *Br. J. Urol.* 1993; **71**: 433-438. [PMID: 8499988]
99. Clemens Q, Calhoun EA, Litwin MS, McNaughton-Collins M, Dunn RL, Crowley EM, Landis JR. Rescoring the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). *Prostate Cancer Prostatic Dis.* 2009; **12**: 285-287. [PMID: 19488065]; [DOI: 10.1038/pcan.2009.22]
 100. Penna G, Mondaini N, Amuchastegui S, Deli inoncenti S, Carini N, Giubilei G, Fibbi B, Colli E, Maqqui M, Adorini L. Seminal plasma cytokines and chemokines in prostate inflammation: interleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. *Eur. Urol.* 2007; **51**: 524-533. [PMID: 16905241]; [DOI: 10.1016/j.eururo.2006.07.016]
 101. Dimitrakov J, Diemer T, Ludwig M, Weidner W. Recent developments in diagnosis and therapy of the prostatitis syndromes. *Curr Opin Urol* 2001; **11**: 87-91. [DOI: 10.1097/00042307-200101000-00013]
 102. Krieger JN, Riley DE, Cheah PY, Liang ML, Yuen KH. Epidemiology of prostatitis: new evidence for a world-problem. *World J. Urol.* 2003; **21**: 70-74 [PMID: 12712363]; [DOI: 10.1007/s00345-003-0329-0]
 103. Nickel JC1, Nigro M, Valiquette L, Anderson P, Patrick A, Mahoney J, Buckley R, Corcos J, Hosking D. Diagnosis and treatment of prostatitis in Canada. *Urol.* 1998; **52**: 797-802. [PMID: 9801102]
 104. Nickel JC, Downey J, Ardern D, Clark J, Nickel K. Failure of a monotherapy strategy for difficult chronic prostatitis/chronic pelvic pain syndrome. *J. Urol.* 2004; **172**: 551-554. [PMID: 15247727]; [DOI: 10.1097/01.ju.0000131592.98562.16]
 105. Elist J. Effects of pollen extract preparation Prostat/Poltit on lower urinary tract symptoms in patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized, double-blind, placebo-controlled study. *Urol.* 2006; **67**: 60-63. [PMID: 16413333]; [DOI: 10.1016/j.urology/2005.07.035]
 106. Kamijo T, Sato S, Kitamura T. Effect of cernitin pollen-extract on experimental nonbacterial prostatitis in rats. *Prostate* 2001; **49**: 122-131.[PMID: 11582591]
 107. Asakawa K, Nandachi N, Satoh S, Honma M, Namikata S, Ishii M, Yasumoto R, Nishisaka N, Masuda G, Kishimoto T. Effects of cernitin pollenextract (Cernilton) on inflammatory cytokines in sex-hormone induced nonbacterial prostatitis rats [in Japanese]. *Hinyokika Kyo* 2001; **47**: 459-65. [PMID: 11523128]
 108. Cai T, Wagenlehner FM, Luciani LG, Tiscione D, Malossini G, Verze P, Mirone V, Bartoletti R. Pollen extract in association with vitamins provides early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome. *Exp. Ther. Med.* 2014; **8**(4): 1032-1038. [PMID: 25187793]; [DOI: 10.3892/etm.2014.1861]
 109. Jolivald CG, Mizisin LM, Nelson A, Ramos KM, Bonke D, Calcutt NA.: B vitamins alleviate indices of neuropathic pain in diabetic rats. *Eur. J. Pharmacol.* 2009; **612**: 4147. [PMID: 19393643]; [DOI: 10.1016/j.ejphar.2009.04.011.028]
 110. Yu CZ, Liu YP, Liu S, Yan M, Hu SJ and Song XJ: Systematic administration of B vitamins attenuates neuropathic hyperalgesia and reduces spinal neuron injury following temporary spinal cord ischaemia in rats. *Eur. J. Pain.* 2014; **18**: 7685. [PMID: 2403859]; [DOI: 10.1002/j.1532-2149.2013.00390x]
 111. Wang ZB, Gan Q, Rupert RL, Zeng YM, Song XJ. Thiamine, pyridoxine, cyanocobalamin and their combination inhibit thermal, but not mechanical hyperalgesia in rats with primary sensory neuron injury. *Pain* 2005; **114**: 266-277. [PMID: 15733653] [DOI: 10.1016/j.pain.2004.12.027]
 112. Hung KL, Wang CC, Huang CY, Wang SJ. Cyanocobalamin, vitamin B12, depresses glutamate release through inhibition of voltage-dependent Ca²⁺ influx in rat cerebrocortical nerve terminals (synaptosomes). *Eur. J. Pharmacol.* 2009; **602**: 230-237. [PMID: 19073169]; [DOI: 10.1016/j.ejphar.2008.11.059]
 113. Carpes ST, Begnini R, Alencar SM, Masson ML. Study of preparations of bee-pollen extracts, antioxidant and antibacterial activity. *Ciência e agrotecnologia.* 2007; **31**(6): 1818-25. [DOI: 10.1590/S1413-70542007000600032]
 114. Bovehl JS, Torrento MS, Lorente EC. Evaluation of polyphenolic and flavonoid compounds in honeybee-collected pollen produced in Spain. *Agr. Food. Chem.* 2001; **49**: 1848-1853. [PMID: 11308335]; [DOI: 10.1021/jf0012300].
 115. Murakami M, Tsukada O, Okihara K, Hashimoto K, Yamada H, Yamaguchi H. Beneficial Effect of Honeybee-collected Pollen Lump Extract on Benign Prostatic Hyperplasia (BPH)-A Double-blind, Placebo-controlled Clinical Trial. *Food Sci. Technol. Res.* 2008; **14** (3): 306-310. [DOI: 10.3136/fstr.14.306]
 116. Xu J, Qian WO, Song JD. A comparative study on different doses of cernilton for preventing the clinical progression of benign prostatic hyperplasia. *Zhonghua Nan Ke Xue.* 2008; **14**: 533-537. [PMID: 18649754].
 117. Qian X, Kong X, Qian Y, Xu D, Liu H, Zhu Y, Guan W, Zheng J, Wang Z, Qi J. Therapeutic efficacy of cernilton in benign prostatic hyperplasia patients with histological prostatitis after transurethral resection of the prostate. *Int. J. Clin. Exp. Med.* 2015; **8**: 11268-11275. [PMID: 26379934].
 118. Winther K., Rein E, Hedman C. Femal, a herbal remedy made from pollen extracts, reduces hot flashes and improves quality of life in menopausal women: a randomized, placebo-controlled, parallel study. *Climacteric* 2005; **8**: 162-170. [PMID: 16096172]; [DOI: 101080/13697130500117987]
 119. Munstedt K, Voss B, Kullmer U, Schneider U, Hubner J. Bee-pollen and honey for the alleviation of hot flushes and other menopausal symptoms in breast cancer patients. *Mol. Clin. Oncol.* 2015; **3**: 869-874.[PMID: 26171198]; [DOI: 10.3892/mco.2015.559]
 120. Kolesarova A, Bakova Z, Capcarova M, Galik B, Juracek M, Simko M, Toman R, Sirotkin AV. Consumption of bee-pollen affects rat ovarian functions. *J. Anim. Physiol. Anim. Nutr. (Berl).* 2013; **97**: 1059-1065. [PMID: 23137268]; [DOI: 10.1111/jpn.12013]
 121. Maughan RJ, Evans SP. Effects of pollen extract upon adolescent swimmers. *Br. J. Sports Med.* 1982; **16**(3): 142-145. [DOI: 10.1136/bjism.16.3.142]
 122. Pascoal A, Rodrigues S, Teixeira A, Feás X, Estevinho LM. Biological activities of commercial bee pollens: Antimicrobial, antimutagenic, antioxidant and anti-inflammatory. *Food Chem. Toxicol.* 2014; **63**: 233-239. [DOI: 10.1016/j.fct.2013.11.010]
 123. Morais M, Moreira L, Feás X, Estevinho LM. Honeybee-collected pollen from five Portuguese Natural Parks: Palynological origin, phenolic content, antioxidant properties and antimicrobial activity. *Food Chem. Toxicol.* 2011; **49**(5): 1096-1101.[DOI: 10.1016/j.fct.2011.01.020]
 124. Komosinska-Vassev K, Olczyk P, Kaźmierczak J, Mencner L, Olczyk K. Bee pollen: chemical composition and therapeutic application. *Evid. Based Complement. Alternat. Med.* 2015; 2015. [DOI: 10.1155/2015/297425]
 125. Salles J, Cardinault N, Patrac V, Berry A, Giraudet C, Collin ML, Chanet A, Tagliaferri C, Denis P, Pouyet C, Boirie Y. Bee-pollen improves muscle protein and energy metabolism in malnourished old rats through interfering with the Mtor signaling pathway and mitochondrial activity. *Nutrients* 2014; **6**(12): 5500-5516. [DOI: 10.3390/nu6125500]
 126. Roubenoff R. Molecular basis of inflammation: relationships between catabolic cytokines, hormones, energy balance, and muscle. *J. Parenter. Enteral. Nutr.* 2008; **32**(6): 630-632. [DOI: 10.1177/0148607108324875]
 127. Lanza IR, Zabielski P, Klaus KA, Morse DM, Heppelmann CJ, Bergen HR, Dasari S, Walrand S, Short KR, Johnson ML, Robinson MM. Chronic caloric restriction preserves mitochondrial

- function in senescence without increasing mitochondrial biogenesis. *Cell Metab.* 2012; **16**(6): 777-88. [DOI: 10.1016/j.cmet.2012.11.003]
128. Osowska S, Duchemann T, Walrand S, Paillard A, Boirie Y, Cynober L, Moinard C. Citrulline modulates muscle protein metabolism in old malnourished rats. *Am. J. Physiol. Endocrinol. Metab.* 2006; **291**: E582-E586. [DOI: 10.1152/ajpendo.00398.2005]
 129. Crozier SJ, Kimball SR, Emmert SW, Anthony JC, Jefferson LS. Oral leucine administration stimulates protein synthesis in rat skeletal muscle. *J. Nutr.* 2005; **135**: 376-382.
 130. Le Plénier S, Walrand S, Noirt R, Cynober L, Moinard C. Effects of leucine and citrulline versus non-essential amino acids on muscle protein synthesis in fasted rat: a common activation pathway? *Amino Acids* 2012; **43**(3): 1171-8. [DOI: 10.1007/s00726-011-1172-z]
 131. Estevinho LM, Rodrigues S, Pereira AP, Feás X. Portuguese bee pollen: palynological study, nutritional and microbiological evaluation. *Int. J. Food Sci. Technol.* 2012; **47**(2): 429-435. [DOI: 10.1111/j.1365-2621.2011.02859.x]
 132. Marzani B, Balage M, Vénien A, Astruc T, Papet I, Dardevet D, Mosoni L. Antioxidant supplementation restores defective leucine stimulation of protein synthesis in skeletal muscle from old rats. *J. Nutr.* 2008; **138**: 2205-2211. [DOI: 10.3945/jn.108.094029]
 133. Feng XT, Wang TZ, Chen Y, Liu JB, Liu Y, Wang WJ. Pollen Typhae total flavone improves insulin-induced glucose uptake through the beta-arrestin-2-mediated signaling in C2C12 myotubes. *Int. J. Mol. Med.* 2012; **30**: 914-922. [DOI: 10.3892/ijmm.2012.1061]
 134. Biolo G, Fleming RD, Wolfe RR. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. *J. Clin. Investig.* 1995; **95**(2): 811-819. [DOI: 10.1172/JCI117731]
 135. Zangarelli A, Chanseume E, Morio B, Brugere C, Mosoni L, Rousset P, Giraudet C, Patrac V, Gachon P, Boirie Y, Walrand S. Synergistic effects of caloric restriction with maintained protein intake on skeletal muscle performance in 21-month-old rats: A mitochondria-mediated pathway. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* 2006; **20**: 2439-2450. [DOI: 10.1096/fj.05-4544com]
 136. Gojda J, Patkova J, Jacek M., Potockova J, Trnka J, Kraml P, Andel M. Higher insulin sensitivity in vegans is not associated with higher mitochondrial density. *Eur. J. Clin. Nutr.* 2013; **67**: 1310-1315. [DOI: 10.1038/ejcn.2013.202]
 137. Hüttemann M, Lee I, Grossman LI, Doan JW, Sanderson TH. Phosphorylation of mammalian cytochrome c and cytochrome c oxidase in the regulation of cell destiny: Respiration, apoptosis, and human disease. *Adv. Exp. Med. Biol.* 2012; **748**: 237-264. [DOI: 10.1007/978-1-4614-3573-0_10]
 138. Šarić A, Balog T, Sobočanec S, Kušić B, Šverko V, Rusak G, Likić S, Bubalo D, Pinto B, Reali D, Marotti T. Antioxidant effects of flavonoid from Croatian *Cystus incanus* L. rich bee pollen. *Food Chem. Toxicol.* 2009; **47**: 547-554. [DOI: 10.1016/j.fct.2008.12.007]
 139. Yıldız O, Can Z, Saral Ö, Yuluğ E, Öztürk F, Aliyazıcıoğlu R, Canpolat S, Kolaylı S. Hepatoprotective potential of chestnut bee-pollen on carbon tetrachloride-induced hepatic damages in rats. *Evid. Based Complement. Alternat. Med.* 2013; **2013**: 461478. [DOI: 10.1155/2013/461478.4]
 140. Viuda-Martos M, Ruiz-Navajas Y, Fernandez-Lopez J, Perez-Alvarez JA. Functional properties of honey, propolis, and royal jelly. *J. Food Sci.* 2008; **73**: R117-124. [PMID: 19021816]; [DOI: 10.1111/j.1750-3841.2008.00966x]
 141. Ishikawa Y, Tokura T, Nakano N, Hara M, Niyonsaba F, Ushio H, Yamamoto Y, Tadokoro T, Okamura K, Ogawa H. Inhibitory effect of honey bee-collected pollen on mast cell degranulation *in vivo* and *in vitro*. *J. Med. Food.* 2008; **11**: 14-20. [PMID: 18361733]; [DOI: 10.1089/jmf.2006.163]
 142. Paulino N, Abreu SRM, Uto Y, Koyama D, Nagasawa H, Hori H, Dirsch VM, Vollmar AM, Scremin A, Bretz WA. Anti-inflammatory effects of a bioavailable compound, Artepillin C, in Brazilian propolis. *Eur. J. Pharmacol.* 2008; **587**: 296-301. [PMID: 18474366]; [DOI: 10.1016/j.ejphar.2008.02.067]
 143. He YM, Wang WJ, Chen WH, Ying J, He CY, Ma YY, Liu Y, Li YS. Effects of Pollen Typhae total flavone on glucose and lipid metabolism in 3T3-L1 adipocytes. *J. Chinese Integr. Med.* 2006; **4**(6): 593-595. [DOI: 10.3736/jcim20060610]
 144. Yamaguchi M, Uchiyama S, Nakagawa T. Anabolic effects of bee-pollen *Cistus ladaniferus* extract on bone components in the femoral-diaphyseal and -metaphyseal tissues of rats *in vitro* and *in vivo*. *J. Health Sci.* 2006; **52**: 43-49. [DOI: 10.1248/jhs.53.625]
 145. Yamaguchi M, Hamamoto R, Uchiyama S, Ishiyama K, Hashimoto K. Preventive effects of bee-pollen *Cistus ladaniferus* extract on bone loss in ovariectomized rats *in vivo*. *J. Health Sci.* 2007; **53**: 571-575. [DOI: 10.1248/jhs.53571]
 146. Kubota Y, Umegaki K, Tanaka N, Kagota S, Nakamura K, Kunitomo M, Shinozuka K. Anti-hypertensive effects of Brazilian propolis in spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol.* 2004; **31**: suppl 2: S29-30. [PMID: 15649281]; [DOI: 10.1111/j.1440-1681.2004.04113x]
 147. Iio K, Ohguchi K, Inoue H, Maruyama H, Araki Y, Nozawa Y, Ito M. Ethanolic extracts of Brazilian red propolis promote adipocyte differentiation through PPAR α activation. *Phytomedicine* 2010; **17**: 974-979. [PMID: 20382515]; [DOI: 10.1016/j.phymed.2010.03.001]
 148. Ikeda R, Yanagisawa M, Takahashi N, Kawada T, Kumazawa S, Yamaotsu N, Nakagome I, Hirono S, Tsuda T. Brazilian propolis-derived components inhibit TNF- α -mediated down-regulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. *Biochim. Biophys. Acta.* 2011; **1810**: 695-703. [PMID: 21554928]; [DOI: 10.1016/j.bbagen.2011.04.007]
 149. Choi SS, Cha BY, Iida K, Lee YS, Yonezawa T, Teruya T, Nagai K, Woo JT. Artepillin C, as a PPAR α ligand, enhances adipocyte differentiation and glucose uptake in 3T3-L1 cells. *Biochem. Pharmacol.* 2011; **81**: 925-933. [PMID: 21219874]; [DOI: 10.1016/j.bcp.2011.01.002]
 150. Guimaraes NSS, Mello JC, Paiva JS, Bueno PCP, Berreta AA, Torquato RJ, Nantes IL, Rodrigues T. *Baccharis dracunculifolia*. the main source of green propolis, exhibits potent antioxidant activity and prevents oxidative mitochondrial damage. *Food Chem. Toxicol.* 2012; **50**: 1091-1097. [PMID: 22119782]; [DOI: 10.1016/j.fct.2011.11.014]
 151. Ueda M, Hayashibara K, Ashida H. Propolis extract promotes translocation of glucose transporter 4 and glucose uptake through both PI3K- and AMPK-dependent pathways in skeletal muscle. *Biofactors* 2013; **39**: 457-466. [PMID: 23355380]; [DOI: 10.1002/biof.1085]
 152. Kwon TD, Lee MW, Kim KH. The effect of exercise training and water extract from propolis intake on the antioxidant enzymes activity of skeletal muscle and liver rats. *J. Exerc. Nutr. Biochem.* 2014; **18**: 9-17. [DOI: 10.5717/jenb.2014.18.1.9]
 153. Teles F, da Silva T, da Cruz Junior FP, Honorato VH, de Oliveira Costa H, Barbosa AP, de Oliveira SG, Porfirio Z, Liborio AB, Borges RL, Fanelli C. Brazilian red propolis attenuates hypertension and renal damage in 5/6 renal ablation model. *PLoS One* 2015; **10**: e0116535. [PMID: 25607548]; [DOI: 10.1371/journal.pone.0116535]
 154. Paulino N, Abreu SRL, Uto Y, Koyama D, Nagasawa H, Hori H, Dirsch VM, Vollmar AM, Scremin A, Bretz WA. Anti-inflammatory effects of a bioavailable compound, Artepillin C, in Brazilian propolis. *Eur. J. Pharmacol.* 2008; **587**: 296-301. [PMID: 18474366]; [DOI: 10.1016/j.ejphar.2008.02.067]
 155. Chirumbolo S. Anti-inflammatory property of propolis. *J. Clin. Biochem. Nutr.* 2015; **56**: 163-164. [PMID: 25759523]; [DOI:

- 10.3164/jcbrn.14-110]
156. Soroy L, Bagus S, Yongkie IP, Djoko W. The effect of an unique propolis compound (Propoelix™) on clinical outcomes in patients with dengue hemorrhagic fever. *Infect. Drug Resist.* 2014; **7**: 323-329. [DOI: 10.2147/IDR.S71505]
 157. Aral CA, Kesim S, Greenwell H, Kara M, Cetin A, Yakan B. Alveolar bone protective and hyperglycemic effects of systemic propolis treatment in experimental periodontitis and diabetes mellitus. *J. Med. Food.* 2015; **18**: 195-201. [PMID: 25265086]; [DOI: 10.1089/jmf.2013.3137]
 158. Baykara M, Silici S, Ozcelik M, Guler O, Erdogan N, Bilgen M. In vivo nephroprotective efficacy of propolis against contrast-induced nephropathy *Diagn. Interv. Radiol.* 2015; **21**: 317-321. [PMID: 26027766]; [DOI: 10.5152/dir.2015.14075]
 159. Elissa LA, Elsherbiny NM, Magmomah O. Propolis restored adiponectin level in type 2 diabetes through PPAR α activation *Egyptian J. Basic Appl. Sci.* 2015; **2**: 318-326. [DOI: 10.1016/j.ejbas.2015.06.003]
 160. Machado BAS, Silva RPD, Barreto GdA, Costa SS, Silva DFD, Brandao HN, Carneiro da Rocha JL, Dellagostin OA, Henriques JAP, Umsza-Guez MA, Padilha FF. Chemical composition and biological activity of extracts obtained by supercritical extraction and ethanolic extraction of brown, green and red propolis derived from different geographic regions in Brazil. *PLoS One* 2016; **11**: e0145954. [DOI: 10.1371/journal.pone.0145954]
 161. Abdulrhman M, Elbarbary NS, Ahmed AD, Saeid ER. Honey and a mixture of honey, beeswax, and olive-propolis extract in treatment of chemotherapy-induced oral mucositis: a randomized controlled pilot study. *Pediatr. Hematol. Oncol.* 2012; **29**: 285-292. [PMID: 22475306]; [DOI: 10.3109/08880018.2012.669026]
 162. Tomazevic T, Jazbec J. A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. *Complement. Ther. Med.* 2013; **21**: 306-312. [PMID: 23876561]; [DOI: 10.1016/j.ctim.2013.04.002]
 163. Noronha VR, Araujo GS, Gomes RT, Iwanaga SH, Barbosa MC, Abdo EN, Ferreira e Ferreira E, Vianan Campos AC, Souzan AA, Abreu SR, Santos VR. Mucoadhesive propolis gel for prevention of radiation-induced oral mucositis. *Curr. Clin. Pharmacol.* 2014; **9**: 359-364. [PMID: 24502424]; [DOI: 10.2174/1574884709666140205210051]
 164. Prabhakar AR, Karuna YM, Yavagal C, Deepak BM. Cavity disinfection in minimally invasive dentistry-comparative evaluation of *Aloe vera* and propolis: A randomized clinical trial. *Contemp. Clin. Dent.* 2015; **6**(Suppl 19): S24-31. [PMID: 25821369]; [DOI: 10.4103/0976-237x.152933]
 165. Choi JH, Jang YS, Oh JW, Kim CH, Hyun IG. Bee pollen-induced anaphylaxis: a case report and literature/ Review *Allergy Asthma Immunol. Res.* 2015; **7**: 513-517. [PMID: 25749764]; [DOI: 10.4168/aa.2015.7.5.513]
 166. Jagdis A, Sussman G. Anaphylaxis from bee-pollen supplement. *Can. Med. Assoc. J.* 2012; **184**(10): 1167-9. [DOI: 10.1503/ema.112181]
 167. Simon A, Traynor K, Santos K, Blaser G, Bode U, Molan P. Medical honey for wound care-still the 'latest resort' *Evid-Based Complement. Altern. Med.* 2009; **6**: 165-173. [DOI: 10.1093/ecam/nem175]
 168. Al-Waili N, Salom K, Al-Ghamdi A, Ansari MJ. Antibiotic, pesticide, and microbial contaminants of honey: human health hazards. *Sci. World J.* 2012; 2012. article ID: 930849
 169. Alvarez-Suarez JM, Tulipani S, Diaz D, Estevez Y, Romandini S, Giampieri F, Damiani E, Astolfi P, Bompadre S, Battino M. 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**(8): 2490-2499. [DOI: 10.1016/j.fct.2010.06.021]
 170. Alvarez-Suarez JM, González-Paramás AM, Santos-Buelga C, Battino M. Antioxidant characterization of native monofloral Cuban honeys. *J. Agric. Food Chem.* 2010; **58**(17): 9817-9824. [DOI: 10.1021/jf101816q]
 171. da Silva PM, Gauche C, Gonzaga LV, Costa AC, Fett R. Honey: Chemical composition, stability and authenticity. *Food Chem.* 2016; **196**: 309-323. [DOI: 10.1016/j.foodchem.2015.09.051]
 172. Pasini F, Gardini S, Marazzan GL, Caboni MF. Buckwheat honeys: screening of composition and properties. *Food Chem.* 2013; **141**(3): 2802-2811. [DOI: 10.1016/j.foodchem.2013.05.102]
 173. Liou GY, Storz P. Reactive oxygen species in cancer. *Free Radic. Res.* 2010; **44**(5): 479-496. [DOI: 10.3109/10715761003667554]
 174. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002; **420**(6917): 860-867. [DOI: 10.1038/nature01322]
 175. Porcza LM, Simms C, Chopra M. Honey and cancer: current status and future directions. *Diseases.* 2016; **4**(4): 30. [DOI: 10.3390/diseases4040030]
 176. Gorjanović SŽ, Alvarez-Suarez JM, Novaković MM, Pastor FT, Pezo L, Battino M, Sužnjević DŽ. Comparative analysis of antioxidant activity of honey of different floral sources using recently developed polarographic and various spectrophotometric assays. *J Food Compos. Anal.* 2013; **30**(1): 13-18. [DOI: 10.1016/j.jfca.2012.12.004]
 177. Alvarez-Suarez JM, Giampieri F, González-Paramás AM, Damiani E, Astolfi P, Martinez-Sanchez G, Bompadre S, Quiles JL, Santos-Buelga C, Battino M. Phenolics from monofloral honeys protect human erythrocyte membranes against oxidative damage. *Food Chem. Toxicol.* 2012; **50**(5): 1508-1516. [DOI: 10.1016/j.fct.2012.01.042]
 178. Kassim M, Achoui M, Mustafa MR, Mohd MA, Yusoff KM. Ellagic acid, phenolic acids, and flavonoids in Malaysian honey extracts demonstrate in vitro anti-inflammatory activity. *Nutr. Res.* 2010; **30**(9): 650-659. [DOI: 10.1016/j.nutres.2010.08.008]
 179. Bertonec J, Doberšek U, Jamnik M, Golob T. Evaluation of the phenolic content, antioxidant activity and colour of Slovenian honey. *Food Chem.* 2007; **105**(2): 822-828. [DOI: 10.1016/j.foodchem.2007.01.060]
 180. Vallianou NG, Gounari P, Panagos J, Kazazis C. Honey and its anti-inflammatory, anti-bacterial and anti-oxidant properties. *Gen. Med.* 2014; **2**: 132-136. [DOI: 10.4172/2327-5146.1000132]
 181. Van den Berg AJ, Van den Worm E, Ufford V, Quarles HC, Halkes SB, Hoekstra MJ, Beukelman CJ. An *in vitro* examination of the antioxidant and anti-inflammatory properties of buckwheat honey. *J. Wound Care.* 2008; **17**(4): 172-179.
 182. Ahmed S, Othman NH. Review of the medicinal effects of tualang honey and a comparison with manuka honey Malays. *J. Med. Sci.* 2013; **20**(3): 6-13.
 183. Sergiel I, Pohl P, Biesaga M. Characterisation of honeys according to their content of phenolic compounds using high performance liquid chromatography/tandem mass spectrometry. *Food Chem.* 2014; **145**: 404-408. [DOI: 10.1016/j.foodchem.2013.08.068]
 184. Chan CW, Deadman BJ, Manley-Harris M, Wilkins AL, Alber DG, Harry E. Analysis of the flavonoid component of bioactive New Zealand mānuka (*Leptospermum scoparium*) honey and the isolation, characterisation and synthesis of an unusual pyrrrole. *Food Chem.* 2013; **141**(3): 1772-1781. [DOI: 10.1016/j.foodchem.2013.04.092]
 185. Moniruzzaman M, Amrah Sulaiman S, Gan SH. Phenolic acid and flavonoid composition of Malaysian honeys. *J. Food Biochem.* 2017; **41**(2). [DOI: 10.1111/jfbc.12282]
 186. Khalil MI, Alam N, Moniruzzaman M, Sulaiman SA, Gan SH. Phenolic acid composition and antioxidant properties of Malaysian honeys. *J. Food Sci.* 2011; **76**(6). [DOI: 10.1111/j.1750-3841.2011.02282.x]
 187. Wiecek J, Pietrzak M, Pomianowski J, Wiecek Z. Honey as a source of bioactive compounds. *Pol. J. Nat. Sci.* 2014; **29**: 275-85.

188. Jaganathan SK, Mandal M. Honey constituents and its apoptotic effect in colon cancer cells. *J. Apipro. Apimed. Sci.* 2009; **1**(2): 29-36.
189. Pichichero E, Cicconi R, Mattei M, Muzi MG, Canini A. Acacia honey and chrysin reduce proliferation of melanoma cells through alterations in cell cycle progression. *Int. J. Oncol.* 2010; **37**(4): 973-981.
190. Swellam T, Miyanaga N, Onozawa M, Hattori K, Kawai K, Shimazui T, Akaza H. Antineoplastic activity of honey in an experimental bladder cancer implantation model: in vivo and in vitro studies. *Int. J. Urol.* 2003; **10**(4): 213-219. [DOI: 10.1046/j.0919-8172.2003.00602.x]
191. Ghashm AA, Othman NH, Khattak MN, Ismail NM, Saini R. Antiproliferative effect of Tualang honey on oral squamous cell carcinoma and osteosarcoma cell lines. *BMC Complement Altern. Med.* 2010; **10**(1): 49. [DOI: 10.1186/1472-6882-10-49]
192. Tahir AA, Sani NF, Murad NA, Makpol S, Ngah WZ, Yusof YA. Combined ginger extract & Gelam honey modulate Ras/ERK and PI3K/AKT pathway genes in colon cancer HT29 cells. *Nutr. J.* 2015; **14**(1): 31-41.
193. Alvarez-Suarez JM, Giampieri F, Cordero M, Gasparrini M, Forbes-Hernández TY, Mazzoni L, Afrin S, Beltrán-Ayala P, González-Paramás AM, Santos-Buelga C, Varela-Lopez A. Activation of AMPK/Nrf2 signalling by Manuka honey protects human dermal fibroblasts against oxidative damage by improving antioxidant response and mitochondrial function promoting wound healing. *J. Funct. Foods* 2016; **25**: 38-49. [DOI: 10.1016/j.jff.2016.05.008]
194. Kaneuchi M, Sasaki M, Tanaka Y, Sakuragi N, Fujimoto S, Dahiya R. Quercetin regulates growth of Ishikawa cells through the suppression of EGF and cyclin D1. *Int. J. Oncol.* 2003; **22**(1): 159-164. [DOI: 10.3892/ijo.22.1.159]
195. Wu J, Omene C, Karkoszka J, Bosland M, Eckard J, Klein CB, Frenkel K. Caffeic acid phenethyl ester (CAPE), derived from a honeybee product propolis, exhibits a diversity of anti-tumor effects in pre-clinical models of human breast cancer. *Cancer Lett.* 2011; **308**(1): 43-53. [DOI: 10.1016/j.canlet.2011.04.012]
196. Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol.* 2007; **35**(4): 495-516. [DOI: 10.1080/01926230701320337]
197. Morales P, Haza AI. Antiproliferative and apoptotic effects of spanish honeys. *Pharmacogn. Mag.* 2013; **9**(35): 231-237.
198. Samarghandian S, Afshari JT, Davoodi S. Honey induces apoptosis in renal cell carcinoma. *Pharmacogn. Mag.* 2011; **7**(25): 46-52.
199. Mantovani A. Cancer: inflaming metastasis. *Nature* 2009; **457**(7225): 36-37. [DOI: 10.1038/457036b]
200. Batumalaie K, Zaman Safi S, Mohd Yusof K, Shah Ismail I, Devi Sekaran S, Qvist R. Effect of gelam honey on the oxidative stress-induced signaling pathways in pancreatic hamster cells. *Int. J. Endocrinol.* 2013; 2013: 367312. [DOI: 10.1155/2013/367312]
201. Safi SZ, Batumalaie K, Qvist R, Mohd Yusof K, Ismail IS. Gelam honey attenuates the oxidative stress-induced inflammatory pathways in pancreatic hamster cells. *Evid-Based Complement. Altern. Med.* 2016; 2016: 5843615. [DOI: 10.1155/2016/5843615]
202. Dvorak HF. Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N. Engl. J. Med.* 1986; **315**: 1650-1659.
203. Gupta MK, Qin RY. Mechanism and its regulation of tumor-induced angiogenesis. *World J. Gastroenterol.* 2003; **9**(6): 1144-1155. [DOI: 10.3748/wjg.v9.i6.1144]
204. Eteraf-Oskouei T, Najafi M, Gharehbagheri A. Natural honey: A new and potent anti-angiogenic agent in the air-pouch model of inflammation. *Drug Res.* 2014; **64**(10): 530-536. [DOI: 10.1055/s-0033-1363229]
205. Kadir EA, Sulaiman SA, Yahya NK, Othman NH. Inhibitory effects of Tualang Honey on experimental breast cancer in rats: A preliminary study. *Asian Pac. J. Cancer Prev.* 2013; **14**: 2249-2254. [DOI: 10.7314/APJCP.2013.14.4.2249]
206. Martin TA, Ye L, Sanders AJ, Lane J, Jiang WG. Cancer Invasion and Metastasis: Molecular and Cellular Perspective. In Madam Curie Biosciences Database; Landes Bioscience: Austin, TX, USA, 2000.
207. Price JT, Thompson EW. Mechanisms of tumour invasion and metastasis: Emerging targets for therapy. *Expert Opin. Ther. Targets* 2002; **6**: 217-233.
208. Oršolić N, Bašić I. Antimetastatic effect of honey. *Mellifera* 2004; **4**: 38-43.
209. Ismail ZB, Alshehabat MA, Hananeh W, Daradka M, Ali JF, El-Najjar EK. Recent advances in topical wound healing products with special reference to honey: A review. *Res. Opin. Anim. Vet. Sci.* 2015; **5**(2): 76-83.
210. Al-Waili, NS. Honey and microbial infections: A review supporting the use of honey for microbial control. *J. Med. Food* 2001; **14**: 1079-96. [DOI: 10.1089/jmf.2010.0161]
211. Mavric E, Wittmann S, Barth G, Henle T. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (*Leptosperm scoparium*) honeys from New Zealand. *Mol. Nutr. Food Res.* 2008; **52**: 483-489. [DOI: 10.1002/mnfr.200700282]
212. Adams CJ, Manley-Harris M, Molan PC. The origin of methylglyoxal in New Zealand manuka (*Leptospermum scoparium*) honey. *Carbohydr. Res.* 2009; **344**: 1050-1053. [DOI: 10.1016/j.carres.2009.03.020]
213. Kwakman PH, Van den Akker JP, Guclu A, Aslami H, Binnekade JM, de Boer L, Boszhard L, Paulus F, Middelhoek P, te Velde AA, Vandenbroucke- Grauls CM, Schultz, MJ, Zaat SA. Medicalgrade honey kills antibiotic-resistant bacteria in vitro and eradicates skin colonization. *Clin. Infec. Dis.* 2008; **46**: 1677-1682.
214. Jervis-Bardy J, Foreman A, Bray S, Tan L, Wormald PJ. Methylglyoxal-infused honey mimics the anti-Staphylococcus aureus biofilm activity of manuka honey: potential implication in chronic rhinosinusitis. *Laryngoscope* 2011; **121**: 1104-1107.
215. Leong AG, Herst PM, Harper JL. Indigenous New Zealand honeys exhibit multiple anti-inflammatory activities. *Innate Immun.* 2012; **8**: 459-466.
216. Cooke J, Dryden M, Patton T, Brennan J, Barrett J. The antimicrobial activity of prototype modified honeys that generate reactive oxygen species (ROS) hydrogen peroxide. *BMC Res. Notes.* 2015; **8**: 20. [DOI: 10.1186/s13104-014-0960-4]
217. Mohd Zohdi R, Abu Bakar Zakaria Z, Yusof N, Mohamed Mustapha N, Abdullah MN. Gelam (*Melaleuca* spp.) honey-based hydrogel as burn wound dressing. *Evid-Based Complement. Altern. Med.* 2011; 2012. article ID: 843025.
218. Nakajima Y, Nakano Y, Fuwano S, Hayashi N, Hiratoko Y, Kinoshita A, Miyahara M, Mochizuki T, Nishino K, Tsuruhara Y, Yokokawa Y, Iuchi T, Kon Y, Mukai K, Kitayama Y, Murakado N, Okuwa M, Nakatani T. Effects of three types of Japanese honey on full-thickness wound in mice. *Evid-Based Complement. Altern. Med.* 2013; 2013. [DOI: 10.1155/2013/504537]
219. Alzubier A, Okechukwu P. Investigation of antiinflammatory, antipyretic and analgesic effect of Yemeni sidr honey. *World Acad. Sci. Eng. Technol.* 2011; **56**: 47.
220. Alandejani T, Marsan J, Ferris W, Slinger R, Chan F. Effectiveness of honey on *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms. *Otolaryngol. Head Neck Surg.* 2009; **141**: 114-118. [DOI: 10.1016/j.otohns.2009.01.005]
221. Nilforoushadeh MA, Jaffary F, Moradi S, Derakhshan R, Haftbaradaran E. Effect of topical honey application along with intralesional injection of glucantime in the treatment of cutaneous leishmaniasis. *BMC Complement. Altern. Med.* 2007; **7**: 13. [DOI: 10.1186/1472-6882-7-13]
222. Yaghoobi R, Kazerouni A, Kazerouni O. Evidence for Clinical Use of Honey in Wound Healing as an Anti-bacterial, Anti-

- inflammatory Anti-oxidant and Anti-viral Agent: A Review. *Jundishapur J. Nat. Pharmac. Prod.* 2013; **8**: 100-104. [DOI: 10.17795/jjnpp-9487]
223. 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**: 2604-2623. [DOI: 10.1111/j.1365-2702.2008.02304.x]
224. Jaganathan SK, Mondhe D, Wani ZA, Pal HC, Mandal M. Effect of honey and eugenol on Ehrlich ascites and solid carcinoma. *J. Biomed. Biotechnol.* 2010; 2010. article ID: 989163.
225. Tomasin R, Cintra Gomes-Marcondes MC. Oral administration of *Aloe vera* and honey reduces walker tumour growth by decreasing cell proliferation and increasing apoptosis in tumour tissue. *Phytother. Res.* 2011; **25**(4): 619-23. [DOI: 10.1002/ptr.3293]
226. Tomasin R, de Andrade RS, Gomes-Marcondes MC. Oral administration of *Aloe vera* (L.) Burm. f.(Xanthorrhoeaceae) and honey improves the host body composition and modulates proteolysis through reduction of tumor progression and oxidative stress in rats. *J. Med. Food.* 2015; **18**(10): 1128-35. [DOI: 10.1089/jmf.2014.0129]
227. EFSA Journal 2010; 8: 1810. www.efsa.europa.eu/efsajournal.htm
228. Silva-Carvalho R, Baltazar F, Almeida-Aguiar C. Propolis: A complex natural product with a plethora of biological activities that can be explored for drug development. *Evid-Based Complement. Altern. Med.* 2015; 2015: 206439. [PMID: 26106433]; [DOI: 10.1155/2015/206439]
229. Noronha VR, Araujo GS, Gomes RT, Iwanaga SH, Barbosa MC, Abdo EN, Ferreira e Ferreira E, Viana Campos AC, Souza AA, Abreu SR, Santos VR. Mucoadhesive propolis gel for prevention of radiation-induced oral mucositis. *Curr. Clin. Pharmacol.* 2014; **9**: 359-364. [PMID: 24502424]; [DOI: 10.2174/1574884709666140205210051]
230. Liskens HF, Jorde W. Pollen as food and medicine: a review. *Economic Bot.* 1997; **51**: 78-87.
231. Nechaeva N. Change of functional and sport medicine after intake of bee products. *Ryazan State Medical University, Ryazan*, in Russia. 2009, pp.1-250.
232. Campos MGR, Frigerio C, Lopes J, Bogdanov S. What is the future of Bee-Pollen? *J. Apipro. Apimed. Sci.* 2010; **2**: 131-144. [DOI: 10.3896/IBRA4.02.4.01]
233. Bogdanov S. Pollen: production, nutrition and health: a review; Bee Products Science. www.bee-hexagon.net, Apl, 20, 2014.