"Apiproduct propolis and diabetes: antioxidant and anti-inflammatory properties of propolis protect against diabetes and diabetes-induced pathologies"

Pr Badiaa Lyoussi
Laboratory of Physiology, Pharmacology and Environmental Health, University Sidi Mohamed Ben Abdallah, Fez, Morocco
E.mail: lyoussi@gmail.com

Abstract

Diabetes mellitus and its associated complications (cardiovascular, renal, hepatic, ophthalmic, neurological, and osteopathic-, endothelial-, and sexual-dysfunction, etc.) remain a burden worldwide in spite of the availability of a number of anti-diabetic drugs, many of which have adverse effects. There is a trend towards using natural products to control hyperglycemia and associated pathologies. Propolis, an apiproduct used by the honeybees as a sealant, has been rediscovered as a medicinal agent, reported to be of benefit in the treatment of allergies, bruises, burns, ulcers, sunburn, wounds, tumors, fatigue, sore throat, nasal congestion, respiratory ailments, flu, colds, acne, skin disorders, and shingles. Propolis consists of plant resins, balsams, wax, bee pollen and essential oils. The composition of propolis (of different colors) depends on the phytogeographical location, seasonal collection time, and botanical source. It is reported to contain more than 300 natural compounds such as polyphenols, phenolic aldehydes, sesquiterpene-quinones, coumarins, amino acids, steroids and inorganic compounds. Propolis is reported to have anti-angiogenic, antihypercholesterolemic, antihypertensive, anti-inflammatory, antimicrobial, antioxidant, anti-parasitic, anti-septic, anti-tumor, antiulcer, anti-viral, immune-stimulatory properties, and hepato-, cardio-, and neuro-protective actions. Diabetes and pathologies associated with it are mainly due to inflammation and oxidative stress, as a result of elevated levels of reactive oxygen species (ROS), which cause lipid peroxidation and protein oxidation. The anti-oxidant, oxygen radical scavenging activity of propolis (and its extracts) is mainly due to the presence of phenolics and flavonoids. The beneficial effects of propolis in diabetes have been confirmed by a number of studies in experimental animals. For example, propolis given orally to rats with streptozotocin (STZ)-induced diabetic rats significantly decreased plasma insulin and insulin resistance, reduced glycated hemoglobin, suppressed elevated hepatic enzymes, and increased hepato-renal glutathione peroxidase levels. An ethanolic extract of propolis administered to STZ-induced diabetic rats, reversed body and kidney weight loss, improved serum glucose and lipid profile, and renal function tests, as well as decreased oxidative damage [increased superoxide dismutase, glutathione, catalase and decreased malondialdehyde (MDA)] in the renal and pancreatic tissue. Similar results were obtained by us using Moroccan propolis in STZ-diabetic rats (unpublished data). Intraperitoneal administration of caffeic acid phenethyl ester (CAPE), an active component of propolis, to STZ-diabetic rats reduced oxidative enzymes and ROS scavengers in the heart tissue.. Incubation of HepG2 cells with propolis blocked the induction of the gene expression and enzyme activity of glucose-6-phosphatase caused by high glucose concentration, suggesting its potential as an antidiabetic agent for the treatment of insulin-sensitive diabetes. The anti-inflammatory action of propolis was demonstrated in a septic shock model in rats (induced by lipopolysaccharide), in which CAPE administration decreased the inflammatory cytokines and increased the anti-inflammatory cytokines levels. Artepillin C, another constituent of

propolis, given orally showed anti-inflammatory effects in mouse model (carrageenan-induced paw edema and peritonitis); the mechanism of action involved prostaglandin E(2) and nitric oxide inhibition through NF-kappaB modulation. The protective role of propolis against the ROS induced damages in diabetic rats and nephrotoxicity models gives hope that they may have similar protective action in humans. Preliminary data in diabetic subjects, which demonstrated beneficial effects of propolis to control and prevent diabetes (unpublished results), and the experimental diabetes study in rodents suggest that propolis (or compounds isolated from propolis) may be useful in human diabetes.

The incidence of diabetes mellitus (DM) is increasing worldwide. Diabetes mellitus, or simply diabetes, is a group of metabolic diseases in which a person has high blood glucose (hyperglycemia), either because the beta cells of pancreas do not produce enough insulin, or because body cells do not respond to the insulin that is produced. There are two main types of DM:
1.Type 1 DM results from insulin deficiency and the patient requires insulin injections. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".
2.Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as “non insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".

Presently there are 371 million (8.3% of population aged 20-79 yr.) diabetics and estimated to be 438 million by year 2030 (International Diabetic Federation); about 97% have type 2 diabetes mellitus (T2DM). 80-85% of T2DM patients have insulin resistance. Impaired β-cell function occurs in 50% of newly diagnosed T2DM, and after that, there is a linear reduction in β-cells with time caused by apoptosis. Diabetes account for 60% of lower limb amputations, 44% of new cases of kidney disease, and is the leading cause of blindness among adults; 65% of deaths occur from cardiovascular disease and strokes in diabetics. Risk factors associated with type 2 diabetes include: Obesity, improper diet and physical inactivity, increasing age, insulin resistance, family history of diabetes and ethnicity. Diabetes mellitus and its associated complications (cardiovascular, renal, hepatic, ophthalmic, neurological, and osteopathic-, endothelial-, and sexual-dysfunction, etc.) remain a burden worldwide in spite of the availability of a number of anti-diabetic drugs, many of which have adverse effects.
Diabetes is a disease of development. Urbanization, changes in lifestyle and developing health systems combine to increase a person’s risk for diabetes substantially. In middle-income countries in particular, the epidemic is hitting younger people and causing death and disability early. People of working age are especially affected which is a serious risk to the economic potential of the countries. As these countries develop and people start to live longer, the epidemic will only increase unless effective prevention and treatment measures are put in place.
Looking at diabetes deaths against spending for diabetes care shows us the impact of a lack of investment very starkly. In countries where very little is spent on diabetes, the rate of death is almost double that in high-income countries where the vast majority of money for diabetes is spent (IDF Diabetes Atlas 5th Edition 2012 Update). Thus, effective strategies, mainly adequate diets, preventing metabolic syndrome are required to de crease the incidence of diseases and promote healthy aging.

It is generally believed that diseases caused by oxidative stress should be treated with apiproducts.. Enhanced oxidative stress in the vascular wall, the heart, the kidney and the brain occurs in cardiovascular disease. It is thus not surprising that there has been interest in testing whether api-product improve diabetes and vascular outcomes. Epidemiological evidence has suggested that some anti-oxidants such as propolis could result in better outcomes. Dietary fruits and vegetables do appear to play a key role in health maintenance and disease prevention.
Several rich sources of polyphenols are able to prevent oxidative stress in the arterial wall by improving the balance between pro-oxidant and anti-oxidant enzymes. They may have these beneficial actions by reducing ROS generation and cardiovascular pathophysiological effects of oxidative stress. This could mean that if anti-oxidants are developed that can also effectively quench oxidative stress in tissues, may be these will indeed improve diabetes .

There is a trend towards using natural products to control hyperglycemia and associated pathologies. Diabetes mellitus promotes overproduction of free radicals reactive oxygen species superoxide anion – which act as – oxidants. These cause diabetes-induced pathologies. The anti-oxidants present in the body offer protection against reactive oxygen species. If the oxidants are more than the anti-oxidants, the body faces oxidative stress. During diabetes, persistent hyperglycemia causes the increased production of free radicals,especially reactive oxygen species (ROS),in all tissues from glucose autoxidation and protein glycozylation. The concentrations of ROS are modulated by antioxidant enzymes and non-enzymatic scavengers such as superoxide dismutase (SOD),catalase (CAT) and glutathione peroxidase (GSH-Px).The three primary scavenging enzymes have been demonstrated in different tissues of diabetic animals.

Propolis is a natural remedy used since antiquity. The first commercial license in 1965 in Romania. Of the 240 commercial licenses, 62% come from Japan. Reference is currently 1,500 articles with the word propolis PubMed.

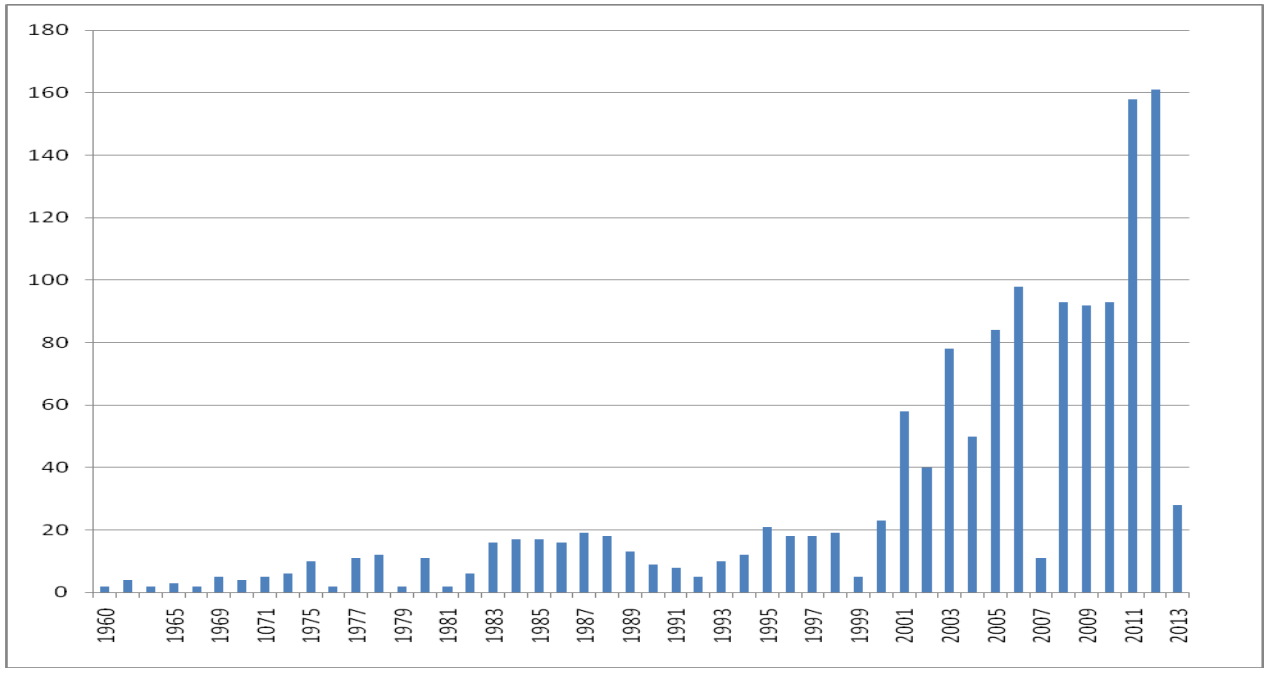

Figure 1 : Evolution of articles number / year related to propolis

Propolis consists of plant resins, balsams, wax, bee pollen and essential oils. The composition of propolis (of different colors) depends on the phytogeographical location, seasonal collection time, and botanical source. It is reported to contain more than 300 natural compounds such as polyphenols, phenolic aldehydes, stilbenes, sesquiterpene-quinones, coumarins, chalcones, flavones, flavonols, flavonoids (galangin, chrysin, caffeic acid phenethyl ester, pinocembrin), amino acids, steroids, and inorganic compounds. Propolis is reported to have anti-angiogenic, antihypercholesterolemic, antihypertensive, anti-inflammatory, antimicrobial, antioxidant, anti-parasitic, anti-septic, anti-tumor, antiulcer, anti-viral, immune-stimulatory properties, and hepato-, cardio-, and neuro-protective activity. Diabetes and pathologies associated with it are mainly due to inflammation and oxidative stress, as a result of elevated levels of reactive oxygen species (ROS), which cause lipid peroxidation and protein oxidation. The anti-oxidant, oxygen radical

scavanging activity of propolis (and its extracts) is mainly due to the presence of phenolics and flavonoids .

Propolis has been used in traditional medicine, cosmetics and food industry from the Europe to East Asia mainly due to the presence of phenolic compounds which have reducing activity, hydrogen-donors and metal chelating properties, among others . Among the phenolic compounds, flavonoids are reported as being responsible for many biological and pharmacological activities, such as antimicrobial, anticancer, anti-inflammatory and antioxidant .

The amounts of total phenolics and flavonoids found in extracts of propolis changed according to the place where they were collected (Table 1). Different regions of Morocco had diverse concentrations of phenols, ranging from a minimal value of 0.74 mg/g for propolis from Kenitra to a maximal of 91.22 mg/g for propolis from Immouzzer. The levels of flavonoids were also significantly different. In this case, the highest concentration was found in the sample from Oujda (34.27 mg/g) and the lowest continued to be the sample from Kenitra (0.20 mg/g).

Table 1. Phenol and flavonoid content in samples of propolis from diverse regions of Morocco obtained by maceration

Sample	Phenol (mg/g)	Flavonoid (mg/g)
Moulay Bouslham	5.98 ± 1.12^{f}	1.75 ± 1.39^{d}
Sidi ifni	6.82 ± 1.12^{f}	1.80 ± 1.39^{d}
Bhalil	12.86 ± 1.12^{e}	3.25 ± 1.39^{d}
Zawiat chikh	5.34 ± 1.12^{fg}	1.87 ± 1.39^{d}
Rabat	53.51 ± 1.12^{c}	33.31 ± 1.39^{a}
Sidi sliman	1.45 ± 1.12^{gh}	0.30 ± 1.39^{d}
Khamissat	65.67 ± 1.12^{b}	12.78 ± 1.39^{c}
Larache	6.00 ± 1.12^{f}	2.05 ± 1.39^{d}
Kenitra	0.74 ± 1.12^{i}	0.20 ± 1.39^{d}
Oujda	44.73 ± 1.12^{d}	34.27 ± 1.39^{a}
Immouzzer	91.22 ± 1.12^{a}	26.30 ± 1.39^{b}
Taza	7.83 ± 1.12^{f}	1.68 ± 1.39^{d}
Taounat	5.89 ± 1.12^{f}	0.93 ± 1.39^{d}
Sefrou	6.211 ± 1.120^{f}	1.05 ± 1.39^{d}

Results are shown as the mean ± SD (n=3). In the same column, values with the same letter are not significantly different (P<0.05).

The antioxidant properties of extracts can be evaluated using diverse in vitro assays. Antioxidant assays in foods and biological systems can be divided in two groups: 1. Those that evaluate lipid peroxidation. 2. Those that measure free radical scavenging ability. In addition, tests evaluating effectiveness against several reactive oxygen species (e. g. superoxide, hydroxyl) are also needed and generally performed. The lipoxygenase assay has been used as an indication of the anti-inflammatory and antioxidant activities. Lipoxygenase catalysed the addition of molecular oxygen to fatty acids containing a cis,cis-1,4-pentadiene system originating an unsaturated fatty acid hydroperoxides. Due to the production of these peroxides, compounds which are able to inhibit that enzyme can be considered as antioxidant. At the same time, those products are converted in others which play a key role in inflammatory processes. Therefore, such compounds which are able to inhibit this enzyme also possess anti-inflammatory properties.

Concerning the antioxidant activities, samples from Khemisset and Imouzzer are good scavengers of active oxygen species, including peroxyl and hydroxyl radicals. These samples are also good scavengers of free radicals like ABTS and showed higher reducing power. Propolis samples from Oujda and Rabat have the best capacity for preventing lipid peroxidation and the last one also presents an anti-inflammatory activity. Some of the propolis samples were also able to inhibit acetylcholinesterase. Overall, these properties can be considered useful to prevent various neurodegenerative diseases, cardiovascular disorders, diabetes and Alzheimer.

A negative correlation was detected between phenols or flavonoids content and capacity for scavenging hydroxyl radicals (Table 2) such as already reported for ABTS and DPPH (Table 2). However, any correlation was found between flavonoids and ORAC values (Table 2). The activity of propolis from Oujda possessing relative high amounts of total phenols (>44 mg/mL) and flavonoids (>34 mg/mL) is weak in contrast to the capacity for scavenging DPPH and ABTS free radicals. The relative good activity of samples from Sidi ifni also contrasts to those found in DPPH and ABTS assays in which weak activities were found.
A negative correlation was observed between phenols and TBARS as well as between flavonoids and TBARS (Table 2).
A negative relationship was found between phenol and lipoxygenase inhibition as well as flavonoid and lipoxygenase inhibition (Table 2).
Propolis from Oujda had the best capacity for inhibiting acetylcholinesterase activity with the lowest IC50 value.. It was possible to detect a negative correlation between phenol and flavonoid content and IC50 values (Table 2)

Table 2 : Pearson correlation coefficients among compounds/antioxidant activities, compounds/acetylcholinesterase inhibition, compounds/lipoxygenase inhibition

	Phenols	**Flavonoids**
DPPH	-0.623**	-0.592**
ABTS	-0.609**	-0.535**
Hydroxyl	-0.743**	-0.647**
TBARS	-0.640**	-0.774**
ORAC	+0.676**	+0.218NS
Lipoxygenase	-0.752**	-0.743**
Acetylcholinesterase	-0.873**	-0.866**

Pearson Correlation significance levels: NS: not significant.
-: Assay not performed
** significant at $P < 0.01$.

A strong correlation was found between the amounts of phenol, flavonoids and antioxidant and anti-inflammatory activities. These results support the hypothesis that phenols contribute greatly to the pharmacological properties of propolis and suggest that propolis could be important in prevention of diseases in which free radicals are implicated.

Streptozotocin, an antibiotic produced by Streptomyces achromogenes, is frequently used to induce DM in experimental animals through its toxic effects on pancreatic β cells. The cytotoxic action of STZ is associated with the generation of ROS causing oxidative damage. In recent years due to the adverse effects of synthetic hypoglycemic drugs,interests in alternate therapeutic approach have became very popular. Nowadays, bee products are gaining popularity in the treatment of diabetes and its complications due to their efficacy, low incidence of side effects and low cost

For example, propolis given orally to rats with streptozotocin (STZ)-induced diabetic rats significantly decreased plasma insulin and insulin resistance (Zamami Y et al., Yakugaku Zasshi 2010;130:833), reduced glycated hemoglobin (Zhu W et al. Human Exp Toxicol 2011;30:1246), suppressed elevated hepatic enzymes (Zhu et al., 2011), and increased hepato-renal glutathione peroxidase levels (Zhu et al., 2011). An ethanolic extract of propolis administered to STZ-induced diabetic rats, reversed body and kidney weight loss, improved serum glucose and lipid profile, and renal function tests, as well as decreased oxidative damage [increased superoxide dismutase, glutathione, catalase and decreased malondialdehyde (MDA)] in the renal (AboSalem OM, et al., Pakistan J Pharm Sci 2009;22:205) and pancreatic tissue (El-Sayed ESM et al., Pakistan J Pharm Sci 2009;22:168).

The aim of our present study was to evaluate the possible protective effects of Ethanolic propolis extract against pancreas β -cells' damage and antioxidant defense systems in streptozotocin induced diabetes rats. Experimental diabetes was induced by a single dose of STZ(65mg/kg)administered by intraperitoneal way. The oxidative stress was measured by tissue MDA levels, proteincarbonyl (PCO) content, reduced glutathione (GSH) content and by enzymatic activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in pancreas. Biochemical observations were further substantiated with histological examination of pancreas.

The increase in blood glucose and MDA levels with the decrease in GSH content and in enzymatic activities were the salient features observed in diabetic rats. Administration of EPE (200mg/kg bw/day) for 30days caused a significant reduction in blood glucose and MDA levels in STZ treated rats when compared with diabetic rats. Furthermore, diabetic rats treated with EP extract showed a significant increase in the activities of both enzymatic and non-enzymatic antioxidants when compared to those of diabetic rats. Degenerative changes of pancreatic β-cells in STZ treated rats were minimized to near normal morphology by administration of EPE as evidenced by histopathological examination. These results clearly indicate that EPE treatment exerts a therapeutic protective nature in diabetes by decreasing oxidative stress and pancreatic β cells' damage which may be attributed to its anti oxidative potential.

Another study protocol tested the effects of Moroccan propolis on streptozotocin-induced type 1 diabetes mellitus in Sprague-Dawley rats. The results showed that Moroccan propolis significantly inhibited body weight loss and blood glucose increase in diabetic rats. In addition, propolis-treated rats showed a significant reduction of glycated hemoglobin levels compared with untreated diabetic rats. Measurement of blood lipid metabolism showed dyslipidemia in diabetic rats and propolis helped to reduce total cholesterol level by 40%. Blood urea nitrogen and urine microalbuminuria-excretion rate demonstrated the beneficial effects of propolis in hepatorenal function. All these results suggested that propolis can alleviate symptoms of diabetes mellitus in rats and these effects may partially be due to their antioxidant ability.

In addition, some compounds contained in propolis might have a potential effect in improvement of insulin sensitivity.
An experimental animals model of diabetes type 2 shows that feeding meriones shawi, a desert rodent with a high-calorie diet induced obesity, diabetes, insulin resistance, and hypertension, which are the hallmarks of metabolic syndrome. This was associated with alteration in vascular reactivity and increased NO release. Strong correlations were observed between weight gain and development of hyperglyceamia, increase in triglycerides and cholesterol plasma levels, while hyperinsulinemia developed after 6 weeks of diet and from then was correlated with weight gain. On the contrary, diabetic meriones exhibited insulinoresistance and improve disturbed glucose metabolism in diabetic Meriones. A marked increase in adipose tissue with larger adipocytes was found in diabetic meriones compared to controls in association with increased epididymal and perirenal adipose masses. 12 weeks high-calorie diet feeding of meriones shawi induced a type 2 diabetes/ metabolic syndrome phenotype associated with hypertension. Intolerance to glucose and insulin resistance were present in this animal model. In addition, our data strongly suggest that iNOS may have a pathogenic role in the development of insulin resistance and diabetes.

We found that propolis improved levels of blood glucose and plasma insulin. In addition, blood pressures were reduced by intake of propolis, which may be caused by a decrease of ENaC-mediated Na^+ reabsorption in the renal tubules via the reduced insulin level. These observations suggest that propolis extracts prevent insulin resistance and the related metabolic and cardiovascular disorders.

The results suggest that dietary supplementation with propolis extract could potentially contribute to nutritional strategies for the prevention and treatment of diabetes mellitus. In conclusion, propolis has a remarkable effect on glucose homeostasis. The ethanol extract of propolis was administered by oral gavage (120 min) at two doses (40 and 100 mg/kg) to anesthetized Wistar rats. Furosemide (10 mg/kg), a standard diuretic was used as the reference drug. Excretion of water and electrolytes (sodium, potassium and chloride) in urine was measured, and glomerular filtration rate (equal to creatinine clearance) was determined. *EPE* increased diuresis, excretion of electrolytes, and glomerular filtration rate in a dose-dependent way; furosemide was more potent as a diuretic and saluretic. The mechanism of action of EPE appears to be similar to that of furosemide. *EPE* possesses diuretic and saluretic activity, thus, validating the use of EPE as a diuretic in Moroccan pharmacopoeia.

The aqueous extract of propolis (AEP) was previously shown to possess a variety of pharmacological activities including anti diabetic and anti-inflammatory activities. Clinical trials in 20 women diabetic volunteers using the AEP showed a marked improvement in glycemic functions and in the severity and frequency of attacks. Preliminary data in diabetic subjects, demonstrating beneficial effects of propolis to control and prevent diabetes, and suggesting that propolis (or compounds isolated from propolis) may be useful in human diabetes
These studies demonstrates that propolis has protective effects against several pathologies. The mechanisms which contribute to its effectiveness involve the quenching of free radicals, increasing antioxidant status and metal-chelating abilities of propolis rich in flavones and esters compounds.

Propolis has been reported to have a broad spectrum of biological activities, has gained popularity also as a health drink and is extensively used in food to improve health and prevent diseases such as inflammation, heart disease, diabetes and even cancer. Because of its broad spectrum of biological activities and its use in food, beverages and folk medicine, there is a renewed interest in the composition and biological activities of propolis.
The proposal mechanisms of action to improve insulinoresistance via several targets as :
Insulin –like / insulin – mimetic activity , Insulinotropic effect, Decrease in insulin resistance/insulin sensitization / enhancement of peripheral glucose utilization, Induction of insulin-like glucose transport into adipocytes , PPAR-γ agonist (glitazone-like) activity: , Dual-PPAR-α/γagonist activity, Increase in binding of GLP-1 to its receptor (Figure 1)

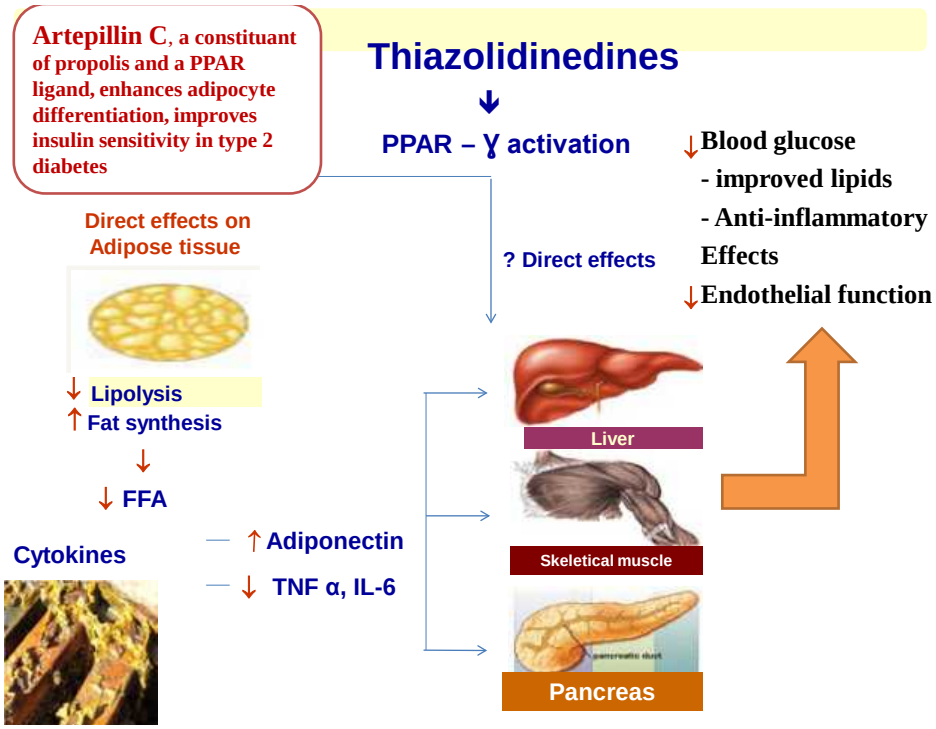

Figure 2: Proposed sites of action of artepillin C, a constituent of propolis in DM. These actions might possibly help preventing DM and its complications.

In conclusion, long term propolis consumption in patients with type 1 DM has the potential to reduce both macrovascular and microvascular complications. Long term propolis therapy in type 2 DM resulted in a decrease in fasting glycemia. Also this reaction was unexpectedly associated with decrease of all macrovascular complications (hypertension and coronary heart disease). On the other hand the macrovascular complications recurred in all patients who stopped propolis therapy and resumed the traditional medicines.

It is strongly recommended to do further clinical trials using propolis alone or in combination with other traditional methods in treatment of patients with diabetes.

References

Abo-Salem OM, El-Edel RH, Harisa GEI, El-Halawany N, Ghonaim MM. Experimental diabetic nephropathy can be prevented by propolis: Effect on metabolic disturbances and renal oxidative parameters. Pakistan J Pharm Sci 2009;22:205-210.

G.A. Burdock, Review of the biological properties and toxicity of bee propolis (propolis), Food Chem. Toxicol., 36 (1998) 347-363.

A.H. Banskota, Y. Tezuka, I.K. Adnyana, E. Ishii, K. Midorikawa, K. Matsushige, S. Kadota, Hepatoprotective and anti-Helicobacter pylori activities of constituents from Brazilian propolis. Phytomedicine, 8 (2001) 16-23.

Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. Fitoterapia 2002;73: S1–S6

L. Chaillou, M.A. Nazareno, Bioactivity of propolis from Santiago del Estero, Argentina, related to their chemical composition, Food Sci. Technol., 42 (2009) 1422-1427.

Dudonne S, Poupard P, Coutiere P, Woillez M, Richard T, Merillon JM, Vitrac X. Phenolic composition and antioxidant properties of poplar bud (*Populus nigra*) extract: individual antioxidant contribution of phenolics and transcriptional effect on skin aging. J Agr Food Chem 2011;59:4527-4536.

El-Sayed E-SM, Abo-Salem OM, Aly HA, Mansour AM. Potential antidiabetic and hypolipidemic effects of propolis extract in streptozotocin-induced diabetic rats. Pakistan J Pharm Sci 2009;22:168-174.

Farooqui T, Farooqui AA. Beneficial effects of propolis on human health and neurological diseases. [Review]. Frontiers Biosci 2012;4:779-793.

Gamal Eldin TA. Propolis can control diabetes and prevents diabetic osteopathy in rats with streptozotocin-induced diabetes. Diabet Technol Therapeut 2011;13:225.

Kang L-J, Lee HB, Bae H-J, Lee S-G. Antidiabetic effect of propolis: Reduction of expression of glucose-6-phosphatase through inhibition of Y279 and Y216 autophosphorylation of GSK-3α/β in HepG2 cells. Phytother Res 2010;24:1554-1561.

Korish AA, Arafa MM. Propolis derivatives inhibit the systemic inflammatory response and protect hepatic and neuronal cells in acute septic shock. Brazilian J Infect Dis 2011;15:332-338.

M.G. Miguel, S. Nunes, S.A. Dandlen, A.M. Cavaco, M.D. Antunes, Phenols and antioxidant activities of hydro-alcoholic extracts of propolis from Algarve, South of Portugal, Food Chem. Toxicol., 48 (2010) 3418-3423.

M.G. Miguel, O. Doughmi, S. Aazza, D. Antunes and B. Lyoussi
Antioxidant, Anti-inflammatory and Acetylcholinesterase Inhibitory Activities of Propolis from Different Regions of Morocco, in press

Okutan H. Ozcelik N. Yilmaz HR. Uz E. Effects of caffeic acid phenethyl ester on lipid peroxidation and antioxidant enzymes in diabetic rat heart. Clin Biochem 2005;38:191-196.

Paulino N, Abreu SR, 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.
J.M. Sforcin, Propolis and the immune system: a review, J. Ethnopharmacol., 113 (2007) 1-14.

G. Papotti, D. Bertelli, L. Bortolotti, M. Plessi, Chemical and functional characterization of Italian propolis obtained by different harvesting methods, J. Agric. Food Chem., 60 (2012) 2852-2862.

Sforcin JM, Bankova V. Propolis: Is there a potential for the development of new drugs? J Ethnopharmacol 2011;133:253-260.

E. Szliszka, Z.P. Czuba, M. Domino, B. Mazur, G. Zydowicz, W. Krol, Ethanolic exctratc of propolis (EEP) enhances the apoptosisinducing potential of TRAIL in cancer cells, Molecules, 14 (2009) 738-754.

Uto Y., Ae S., Koyama D., Sakakibara M., Otomo N., Otsuki M., Nagasawa H., Kirk K.L., Hori H. Artepillin C isoprenomics: Design and synthesis of artepillin C isoprene analogues as lipid peroxidation inhibitor having low mitochondrial toxicity Bioorganic and Medicinal Chemistry 2006 14:16 (5721-5728)

Zamami Y, Fujiwara H, Hosoda M, Hino H, Hirai K, Okamoto K, Jin X, Takatori S, Doi-Takaki S, Kawasaki H. Ameliorative effect of propolis on insulin resistance in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Yakugaku Zasshi 2010;130:833-840.

Zhu W, Li YH, Chen ML, Hu FL. Protective effects of Chinese and Brazilian propolis treatment against hepatorenal lesion in diabetic rats. Human Exp Toxicol 2011;30:1246-1255.

L. Wang, A.N. Wang, S. Mineshita, I. Ga, Anti inflammatory effects of propolis, Jpn. J. Pharmacol. Ther., 24 (1993) 223-226.