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ORIGINAL ARTICLE

VITAMIN E VERSUS PROPOLIS AS AN ADD-ON THERAPY TO SITAGLIPTIN/METFORMIN ON OXIDANT/ANTIOXIDANT STATUS AND LIPID PROFILE IN TYPE 2 DIABETIC PATIENTS

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Summary

The main health care challenges associated with diabetic patients are glycemic control. Insulin defection has been regarded as the mainstay which needs to be tackled to avoid glucose over presence in the circulatory system. These challenges have always been conjoined with the patient's redox status, hence, oxidants/antioxidants determine the fate of pancreatic tissue status and they are reciprocally interrelated. Various remedies have been utilized by patients themselves and healthcare workers to control hyperglycemia if any. Herbal and pharmacological therapy were always being used hand in hand. Herein, we are demonstrating the antioxidant effect of propolis and its role in modulation of lipid profile in type 2 diabetic patients using vitamin E for comparison in sequential mode i.e. vitamin E used for 8 weeks followed one-week washout period and then propolis therapy started in the same group of patients (n = 45). Thereby a sample of serum has been collected in the first visit (baseline and vitamin E started, followed by collecting serum after 8 weeks (second visit); followed by commencing of propolis after a washout week from the second visit, at the third visit another serum sample collected from all patients. Serum was analyzed for oxidant/antioxidant status represented by malondialdehyde (MDA) and total antioxidant status (TAS). Additionally, lipid profile has been measured from the same samples. The results indicate that both propolis and vitamin E positively modulated the measured parameters with superiority of propolis over vitamin E in improving these measured biomolecules. To conclude, propolis is an overall safe natural product and is inducing such positive effects in the diabetic patient, we do advise these patients to start propolis therapy as an adjuvant medication to control these deleterious biomolecules.

Key words: Vitamin E; Propolis; Sitagliptin; Lipid; TAS; MDA; Diabetes

Introduction

"Type 2 diabetes mellitus (T2DM)" is a systemic condition of elevated glucose levels caused by insufficient insulin signaling in "insulin-sensitive cells" and irregular insulin production. The number of persons "diagnosed

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with T2DM" is rapidly growing. T2DM affects 6 % of the population in the United States, Europe, and most Westernized nations (1). The rate in China's major cities approaches 6 % (2). As per a commonly recognized estimate, the proportion of diabetes patients (most of whom have T2DM) might reach (366 million by 2030), owing to an increase in the prevalence of overweight and "a sedentary lifestyle" (3).

T2DM, particularly its growing comorbidities, has a very bad prognosis and may result in a significant decline in average lifespan. The total cost of healthcare with T2DM and related consequences is quite expensive, according to economic analyses of late complications. As a result, significant attention has focused on the creation of alternative medical foods, including the screening of "natural bioactive chemicals" with the capacity to enhance glucose management and reduce the risk of problems (4, 5).

"Propolis is a natural substance" that is safe to consume. It is a "resinous hive material" gathered by "honeybees" from numerous plant sources. It is a popular traditional medicine with a wide range of biological activities (6–10). Many studies in recent years have found that propolis has hypoglycemic action (11–13) and has some beneficial effects on diabetes complications (14, 15). Propolis was studied for its ability to withstand oxidative damage (16), boost body immunity, and impact metabolic enzymes to show its therapeutic benefits on diabetes mellitus (17).

In T2DM rats, "glycometabolism, lipid metabolism, and insulin resistance" are all unknown. Earlier studies have shown that propolis ethanol and water extracts have a beneficial impact on diabetic mice (18–20). Nevertheless, because propolis is a highly sticky, resinous combination of insoluble or barely soluble chemicals with a bitter taste, its use as a health-promoting agent has been limited (21). An encapsulating technique was employed to increase the solubility and bioavailability of propolis (22). The present study aimed to compare the antioxidant and lipid-modulating effect of vitamin E or propolis on the same patient's samples using a sequential model with a washout period of one week in between vitamin E and propolis.

Material and methods

A total number of 45 type 2 diabetic patients were enrolled in the present study (Table 1). A consent form was taken from conjoined patients to confirm individuals' awareness and acceptance. Patients with other illnesses, smokers, alcoholics, lactating or pregnant women, and patients on drugs other than sitagliptin/metformin were excluded from the study. Starting from December 1st, 2020 to December 1st, 2021, a pre-post -sequential interventional study was conducted at the Diabetic and Endocrinology civil clinic and Diabetic Centre in Mosul, Iraq.

Table 1. Demographic characteristics of type 2 diabetic patients on sitagliptin/metformin therapy at the beginning of the study, [n=45]

Parameter	Mean ± SD
BMI (kg/m^2)	32.90 ± 3.56
Age (years)	54.48 ± 6.16

Included diabetic patients were those who are solely based on combination therapy of sitagliptin/metformin on a dosing schedule of 12-hours intervals basis, for at least 3 months on sitagliptin/metformin therapy. Serum samples were withdrawn from patients on their first visit and after 8-week of vitamin E use (second visit), then the patients were asked to keep a washout period of one week and start propolis for an additional 8 weeks followed by serum sample collection (third visit). It's worthy to mention that we do start our interventional study with 66 patients, unfortunately, 21 patients have dropped out of our study because they did refuse to continue the add-on regimen, details are shown in the workflow diagram below (Figure 1).

The details and origin of used conventional therapy and add-on therapy were mentioned in Table 2.

Patients' adherence to the add-on therapy was taken into consideration using different strategies. The timing of the dose was adjusted to be suitable with the patient's other medication. The dose of either vitamin E or propolis was chosen to be one daily. Patient education was also conducted by discussing the importance of this add-on

therapy to patient overall health. Moreover, weekly phone contact was used to confirm that patients were properly using their medication. The patients were asked to keep empty boxes of add-on therapy and return them in the next visit to count a number of tablets used/left.

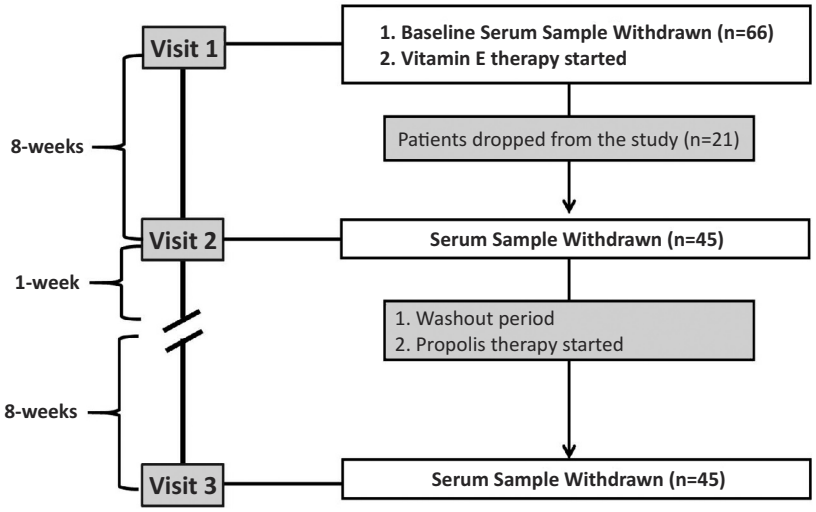

Figure 1. Workflow diagram.

Table 2. Origin and supplier's details of used medication in the present study.

Medications	Trade Name	Suppliers	Dose
Sitagliptin/Metformin	Sitavia plus	Pioneer	50/500 (2 times daily)
Vitamin E	Vitamin E	Adrien Gagnon/ Canada	400 I.U/day
Propolis	Bee Propolis	Lake Avenue Nutrition	1000 mg/day

"Serum malondialdehyde" was measured using a kit supplied by Elabscience (MDA, E-BC-K025-S, USA), the principle of the assay was based on the reaction of the MDA molecule with thiobarbituric acid producing a complex (red-colored); the optical density was measured at 532 nm. According to manufacturer instruction, the procedure was performed by mixing the reagent mixtures with the standard and serum sample in an acidic environment (using kit-supplied glacial acetic acid). The reagent mixture was prepared by dissolving the thiobarbituric acid powder in distilled water, followed by mixing it with glacial acetic acid, this reagent mixture was then cooled down to be stored for future use when samples are ready for analysis.

Serum total antioxidant status (TAS) was measured using a kit supplied by Elabscience (TAS, E-BC-K136-S, USA), the assay was conducted through the mixing of the reaction mixture with the serum and samples resulting in the formation of chromogenic complex formation (pale yellow) and the color darkness is reciprocally related to the antioxidant status which was quantified at an optical density of 520 nm. The principle of the assay is based on reducing Fe^{+3} to Fe^{+2} which will eventually make a complex with phenanthroline chromogen provided by the supplier.

On 6 ml of peripheral circulation obtained from overnight fasted participants, biochemical examination of blood parameters was performed. Serum was collected and stored at -20 degrees Celsius for further examination. "Fasting total serum cholesterol (TC), Triglycerides (TG), and high-density lipoprotein (HDL)" were measured using enzymatic colorimetric techniques using the BIOLABO kit. Cholesterol and its esters are liberated from lipoprotein by detergent cholesterol esterase, which hydrolyzes the esters; H_2O_2 is produced by the enzymatic oxidation of cholesterol by cholesterol oxidase. At 500 nm, the absorbance of the colored complex (Quinoneimine) was measured, which is proportional to the quantity of TC in the material. Lipase hydrolyzes triglycerides, resulting in glycerol and free fatty acids. Glycerol takes part in a chain of events that results in the creation of a pink quinoneimine. At 500 nm, the absorbance of the colored complex (Quinoneimine) was measured.

The precipitation technique was used to estimate serum HDL-C, and a BIOLABO kit was used.

The concentration of high-density lipoprotein in the supernatant after centrifugation was determined using total cholesterol reagent. LDL and VLDL cholesterol levels were determined using customized questions and plotted against the control group.

A one-way analysis of variance (ANOVA) was performed to compare different groups. A mean difference was considered significant at $P < 0.05$. The Bonferroni multiple range tests were used as a post-hoc test.

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Results

Compared to baseline levels (5.77 ± 0.79; 5.774 ± 0.788), serum MDA level was significantly ($p < 0.05$) reduced after administration of either vitamin E (4.763 ± 0.80) or propolis therapy (4.254 ± 0.497) with a percentage reduction of about 18 % and 26 % for vitamin E and propolis, respectively (Figure 2A). Correspondingly, TAS were significantly ($p < 0.05$) elevated after administration of either vitamin E (0.700 ± 0.102) or propolis therapy (0.772 ± 0.086) with percentage elevation of about 23 % and 36 % for vitamin E and propolis, respectively; Compared to baseline levels (0.570 ± 0.096; 0.570 ± 0.096) (Figure 2B). Additionally, significantly higher ($p < 0.05$) levels of TAS and significantly lower levels of MDA were demonstrated in propolis-treated to vitamin E-treated (See Figure 2 A and B).

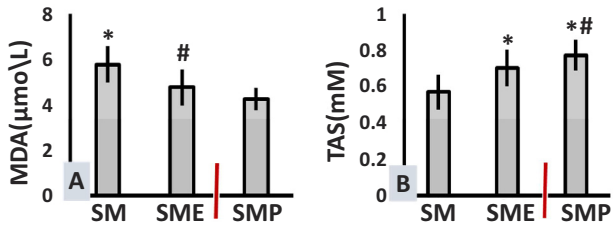

Figure 2. Vitamin E and propolis positively improved redox status in T2DM. Data expressed as mean±SD, *p<0.05 control versus add-on therapy, #p<0.05 vitamin E compared to propolis. S=sitagliptin, M=Metformin, P=propolis, E=Vitamin E, MDA=Malondialdehyde, TAS=Total antioxidant status.

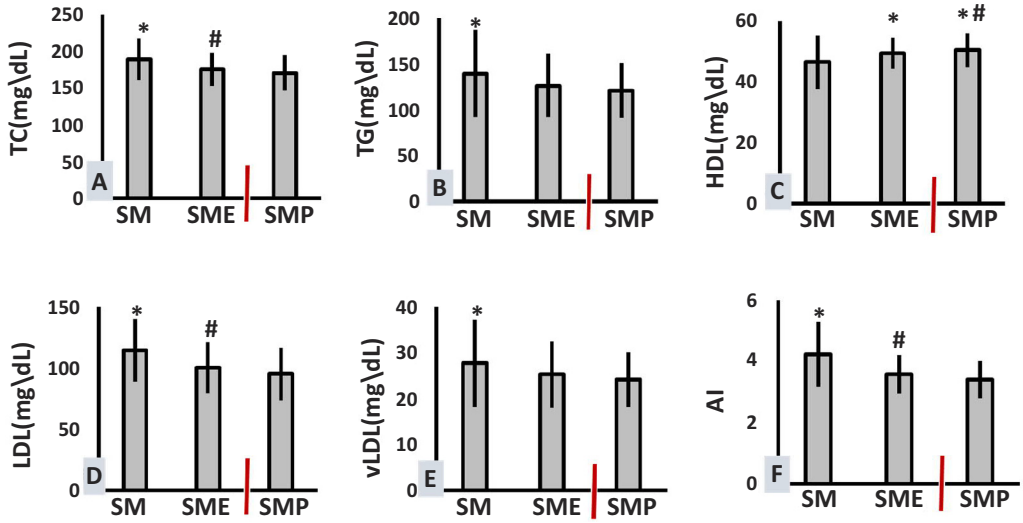

Figure 3. Vitamin E and propolis positively improved lipid profile in T2DM indicated by reduced TC and TG alongside elevated HDL. Data expressed as mean±SD, *p<0.05 control versus add-on therapy, #p<0.05 vitamin E compared to propolis. S=sitagliptin, M=Metformin, E=vitamin E, P=propolis, TC=Total cholesterol, TG=Triglycerides, HDL=High-density lipoprotein, LDL=low-density lipoprotein, vLDL=very low-density lipoprotein, and AI=atherogenic index. Red-bar indicates a washout period of one week.

Compared to baseline levels, serum TC, TG, LDL, and VLDL levels were significantly ($p < 0.05$) reduced after administration of either vitamin E or propolis therapy (Figure 3 A, B, D, E) with a percentage reduction of up to 10 % in both parameters for either propolis or vitamin E, however, slightly higher reduction rates were obtained in the propolis-treated group compared to vitamin E-treated group (Figure 3A, B, D, E). Correspondingly, HDL levels were significantly ($p < 0.05$) elevated after administration of either vitamin E or propolis therapy (Figure 3C) with percentage elevation of up to 8% for either propolis or vitamin E, however, slightly higher elevation rates were obtained in the propolis-treated group compared to vitamin E-treated group. Correspondingly, the atherogenic index was positively improved showing an overall significant reduction in both propolis and vitamin E treated group (Figure 3F).

Discussion

The outcome of the present study has confirmed that sequential using vitamin E followed by propolis as add-on therapy to type 2 diabetes patients has positively regulated redox status and lipid profile in the studied groups compared to the control non-interventional group. The participants of the study were comparably matched regarding demographic parameters and medication prescribed for diabetes (sitagliptin/metformin). Vitamin E and propolis have reduced the serum level of total cholesterol, triglycerides, LDL, and VLDL together with elevation of HDL serum level; correspondingly, the atherogenic index has significantly improved. Additionally, propolis has shown superior positive effect over vitamin E in reducing total cholesterol, LDL, and atherogenic index; together with elevated HDL in propolis-treated compared to vitamin E- treated group.

HDL is a protective lipoparticle against neutrophil lipophagocytic properties, stabilizes LDL against oxidation, and mitigates cardiovascular diseases (23). A randomized controlled clinical trial conducted by Mujica, V. *et al*. 2017, confirmed that 3-month use of propolis has significantly increased HDL level in the general population compared to the placebo-treated group, which are in agreement with our findings (23). However, Zakerkish *et al.*, 2019, confirmed that Iranian propolis has modestly elevated HDL with no effects on TC, TG, LDL, and VLDL in type 2 diabetic patients (24). Nonetheless, a separate Iranian study conducted by Hesami *et al*. 2019, reported a reduction of oxidized LDL levels alongside slightly improved catalase activity in type 2 diabetic patients (25). Fukuda *et al*., found out that using Brazilian propolis associated with no change in redox parameters or lipid profile in type 2 diabetic patients (26). These findings disagree with our results as we reported elevation of HDL and reduction of TC, TG, LDL, and VLDL in propolis treated versus non-treated group. These contradictions in the results could be partly explained in the context of the type of propolis used, degree of glycemic control, and variation in the type of medication used in us versus other studies (24). Alternatively, a randomized, double-blinded, placebo-controlled trial conducted by Afsharpour *et al*. 2019 reported that propolis administration as an adjuvant therapy has been associated with improved glycemic control and promotion of antioxidant status in diabetic patients; through measuring fasting blood sugar, insulin, insulin resistance, hemoglobin A1c, total antioxidant capacity, the activity of glutathione peroxidase, and superoxide dismutase (27).

Vitamin E is "a potent lipid-soluble antioxidant" that lowers "oxidative stress" and the impairment caused by "oxidative stress in T2DM" (28). Vitamin E's anti-hyperglycemic actions have been hypothesized, tested in the laboratory and human investigations, and shown to have biological application. Observation-based research has found that vitamin E use is negatively associated with the incidence of T2DM (29). Additionally, frequent vitamin E intake is connected with a massive improvement in glycemic control in individuals with diagnosed T2DM (30), providing the rationale for research assessing "vitamin E supplementation" and glycemic control in T2DM participants.

In a study conducted by Dávila-Esqueda *et al*., 2005, on in vitro streptozotocin-induced diabetes model using Sprague-Dawley rats to determine the vitamin E effects on lipid parameters; the study concluded that vitamin E has a modest non-significant effect in normalizing cholesterol and triglyceride levels compared to control group (31). A similar study conducted on the experimental rat model by Abo-Salem *et al*. 2009, reported that propolis improved antioxidant status and improved lipid profile in vitro diabetes induced model, moreover, the action reciprocally correlated to the dose of propolis ethanolic extract used (32). This later study is in the line with our results confirming that vitamin E is an effective player for modulating redox status and improving the lipid profile.

"A meta-analysis" of fourteen randomized controlled trials with 714 participants found that "vitamin E supplementation" did not affect "HbA1C, fasting glucose, or fasting insulin levels". Significant variation was seen in all three studied models. Despite that, when the researcher included subpopulations interpretation, to identify the source of heterogeneity; the meta-analysis has come up with a conclusion with decreased plasma vitamin E levels and weaker blood glucose control, subpopulations findings indicate that "vitamin E supplementation" significantly reduced contextual "HbA1c and fasting insulin". Additionally, higher vitamin E dosages and extended trial lengths improved "HbA1c and fasting insulin concentrations". Although the meta-analysis did not find any significant connections between "vitamin E supplements" and improvements in glycemic control, our findings suggest that T2DM patients with low blood "vitamin E concentrations" or poor glycemic control may benefit from vitamin E supplements (33).

Latest molecular investigations on vitamin E's impact on glucose tolerance give more support for the biological validity of these observations. There is now substantial evidence that "oxidative stress" is crucial in the glycation of hemoglobin (34) and "beta-cell damage" (35) in T2DM. In preclinical diabetes, vitamin E, a prevalent antioxidant, reduces ROS production in the pancreas and protects "the structural integrity of pancreatic islets" (36). Additionally, there are indications that vitamin E intake "prevents glycation of hemoglobin", a hallmark for diabetes detection in medical settings, by halting glycosylation at an early point in "the Maillard reaction" (37) or by partially blocking the synthesis of AGEs (38). Furthermore, in addition to its protective benefits, for providing pancreatic preservation from hitting by free radicals induced apoptosis (36).

The major limitation of our study is the short washout period of one week and the reason that we did this, was to avoid patient incompliance; since out of 66 patients enrolled in the study only 45 of them completed the course of the therapy. Another point that is worthy to mention is the limitation of sample size; therefore, larger sample size studies need for further assessments.

Conclusion

The present sequential interventional study confirmed that dualistic use of vitamin E followed by propolis therapy has improved the oxidant-antioxidant status indicated by reducing malondialdehyde and increasing total antioxidant status. The lipid profile has been improved in these patients indicated by reduced cholesterol and triglyceride levels together with increased HDL levels. Accordingly, VLDL, LDL, and atherogenic index are modulated. We do advise using propolis and vitamin E in such patients.

Acknowledgment

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Conflict of Interest

The authors declare that no conflict of interest exists for this research.

Adherence to Ethical Standards

The study was approved by the Medical Research Ethics Committee in the university of Mosul, the study approval number and date UOM/COM/MREC/2020-2021 (32) on 07/04/2021.

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