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ANTI-INFLAMMATORY, ANTIOXIDANT, AND VASODILATING EFFECT OF EVENING PRIMROSE OIL IN TYPE 2 DIABETIC PATIENTS

Mustafa Safaahussain [1], Manal Khalid Abdulridha [* 2] and Mahmood Shaker Khudhair [3]

AL-Kadhimiyah Hospital [1], Ministry of Health, Iraq.
Department of Clinical Pharmacy [2], College of Pharmacy, Al-Mustansiriya University, Iraq.
Consultant Endocrenologist [3], Department of Internal Medicine, College of Medicine, Al-Nahrain University, Iraq.

ABSTRACT: Type 2 diabetes mellitus (T2DM) consider the most common diseases in modern societies. Natural products or compounds reported as useful remedies for controlling or preventing T2DM are categorized into 5 major groups namely, anti-inflammation products, AMPK activators, insulin secretion stimulators, alpha-glucosidase/ disaccharidase or amylase inhibitors and products acting with an unknown mechanism. Evening primrose oil is a substantial source of omega-6 essential fatty acids, mostly gamma-linolenic acid (GLA)). Linolenic acid (LA) forms GLA by Δ-6-desaturase enzyme. The activity of Δ-6-desaturase enzyme, which is compromised in patients with type 2 diabetes. Accordingly, this study aims to evaluate the effect of evening primrose oil in reducing the complications of type 2 diabetes mellitus. Twenty-Six Iraqi patients newly diagnosed with type 2 diabetes who are either overweight or obese. Thirteen patients received metformin 500 mg tablets twice daily alone, and 13 patients received metformin 500 mg plus evening primrose oil 2 gm capsule twice daily for 3 month therapy. Serum hs-CRP, Tumor necrosis factor α, and malondialdehyde (MDA) were measured. There was a statistically significant elevation in baseline levels of serum MDA, hs-CRP, and TNF-α, and in both systolic and diastolic blood pressure in both patient groups compared to control subjects, ($P<0.001$). High reduction after 3 months of treatment was found in these parameters compared to pretreatment level, significantly with serum MDA, TNF-α, and in both systolic and diastolic BP in patients group receiving evening primrose oil ($P<0.001$). It can be concluded that early intervention with natural oil rich in gamma-linolenic acid, which possesses anti-angiogenic, anti-inflammatory, and anti-oxidant activities, with traditional hypoglycemic drugs can improve therapeutic benefits and represent a promising strategy to restrain the progression of diabetes complications.

Keywords: Evening primrose-Oenothera biennis, Type 2 diabetes mellitus, anti-anti-inflammatory, anti-oxidant activities

Correspondence to Author:
Manal Khalid Abdulridha

Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq.

E-mail: pharm.mrdha@uomustansiriyah.edu.iq

INTRODUCTION: Type 2 diabetes mellitus (T2DM) consider the most common diseases in modern societies [1].

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The prevalence of type 2 diabetes mellitus is increasing worldwide, parallel to the current obesity epidemic [2]. Nearly 23% of patients with morbid obesity have type 2 diabetes, and the spread of screening-detected diabetes is 8% [2].

The universal epidemic of T2DM is tied to rising rates of overweight and obesity in adults as well as in youth [3]. Many of oral anti-diabetic agents have been developed through the last 40 years [4].

Safety considerations must always be carefully considered with the selection of the hypoglycemic agents [5]. Development and use of natural products as therapeutic agents, especially those prepared from plants, have been intensified in recent years. Some naturally occurring anti-hyperglycemic phytochemicals have been suggested as potential drugs for the treatment of T2DM [6]. Natural products or compounds reported as useful remedies for controlling or preventing T2DM are categorized into 5 major groups namely, anti-inflammation products, AMPK activators, insulin secretion stimulators, alpha-glucosidase/ disaccharidase or amylase inhibitors and products acting with an unknown mechanism [6].

Evening primrose- *Oenothera biennis* is a prevalent plant, which exists in the temperate regions of North America, Europe, and South America. Evening primrose is a wildflower that belongs to the genus of *Oenothera* [7]. Historically, evening primrose (*Oenothera* spp.) has been grown both as a charming wildflower and as an herbal supplement. Increasingly, evening primrose oil (EPO) has been recognized by the medical society as a valid health care product [8].

Evening primrose was a fundamental food for many Native American clans and a famine food for Chinese farmers. European settlers and Native Americans used the entire plant to improve ailments such as bruising, stomach aches, and shortness of breath [9]. Evening primrose oil is extracted from the seeds of *Oenothera biennis*. Evening primrose oil is a substantial source of omega-6 essential fatty acids, mostly gamma-linolenic acid (GLA) and linoleic acid (LA), both major components of myelin and the neuronal cell membrane [10].

Researchers have found that the high concentrations of GLA found in evening primrose oil can be used to treat several pathological conditions in humans caused by GLA deficiencies. Supplementation of the diet with the GLA extracted from the oil of plants such as evening primrose is thought to minimize the severity of many diseases [8]. GLA has anti-inflammatory, anti-thrombotic, and lipid-reducing the effect. It also enhances smooth muscle relaxation and vasodilatation. Also, EFAs, including GLA, are substantial constituents of membrane phosphor lipids, including the mitochondrial membrane, where they promote the integrity and fluidity of the membrane [11]. Linolenic acid (LA) forms GLA by Δ-6-desaturase enzyme. GLA forms di-homo-gamma-linolenic acid (DGLA), which can be turned into prostaglandin E1 (PGE1) or to arachidonic acid (AA) by-products (e.g., series 2 prostaglandins [PGE2], leukotrienes, and thromboxane). PGE1 is preferentially created, however, because the conversion from DGLA to arachidonic acid is slower [10]. The activity of Δ-6-desaturase enzyme, which is compromised in patients with type 2 diabetes [10]. The action of this enzyme further decreases with age and in people suffering from diverse diseases, including arthritis, diabetes, hypertension, eczema, psoriasis, and so on. Lifestyle factors like stress, smoking, over-consumption of alcohol, saturated and trans-fatty acids and nutritional deficiencies of Vitamin B6, zinc, and magnesium suppress this desaturase [12]. As a result of restrictions *in vivo* production of GLA, supplementation with preformed GLA is becoming substantial. This has led to attention in the development and commercialization of the sources of GLA [13].

Accordingly, this study aims to evaluate the effect of evening primrose oil in reducing the complications of type 2 diabetes mellitus via its anti-inflammatory and antioxidant consequently reducing the microvascular complications of T2 DM, and also to assess its smooth muscle relaxation and vasodilatation effect by reducing the BP as a risk for other macrovascular complications.

PATIENTS AND METHODS:

Study Design: This is a prospective randomized controlled interventional open-label study to evaluate the efficacy of primrose oil in T2 diabetic patients.

Patients: Twenty-Six Iraqi patients newly diagnosed with type 2 diabetes with age range between (35-60) years. Both genders were eligible for the study. Sixteen patients were female, and 10 patients were male.

Most of the patients are either Overweight having a BMI ranging from (25-29.9) kg/m² or obese with a BMI (≥30) kg/m². Fourteen healthy control subjects

were included in the study. Patients will be treated according to routine clinical practice at the discretion of the treating physician. The eligible patients and subjects were allocated into three main groups:

Group 1: Include 13 patients who have diagnosed type 2 diabetes are assigned to receive metformin 500 mg tablets twice daily alone (as a conventional therapy) for 3 month therapy (as an active comparator).

Group 2: Include 13 patients who have diagnosed type 2 diabetes are assigned to receive metformin 500 mg plus evening primrose oil 2 gm capsule twice daily for 3 month therapy.

Group 3: Include 14 healthy control subjects.

Ethics approval was obtained from the Institutional Scientific Committee.

MATERIALS:

TABLE 1: DRUGS, CHEMICAL, AND THEIR SUPPLIERS

Chemicals and drugs	Suppliers
Kit for serum MDA	Shanghai Yehua Biological Technology Co., Ltd.
Kit for serum TNF alpha	Shanghai Yehua Biological Technology Co., Ltd
Kit for serum human hs-CRP	Cusabio
Glucophage (metformin) 500 mg tablet	Merck
Evening primrose oil 1000 mg soft gel capsule	Vitane

METHODS: All patients were fasting (12-14) h calories free diet. Ten ml of venous blood were drawn using a plastic disposable syringe of 10ml capacity to measure the inflammatory and oxidative stress marker. Serum hs-CRP, Tumor necrosis factor α (TNF-α), and the concentration of human malondialdehyde (MDA) are measured using the enzyme-linked immune sorbent assay (ELISA) [14]. Blood pressure readings were recorded using manual Sphygmomanometer device.

Statistical Analysis: Data were translated into a computerized database structure, and the statistical analyses were carried out using the computer program SPSS version 20 (Statistical Package for Social Sciences-version 20). The results were expressed as mean ± SD. Data were statistically evaluated using a paired *t*-test to compare pre and post-treatment results among the study groups. Values with $P<0.05$ were considered significantly different.

RESULTS AND DISCUSSION:

1. Patients Demographic Characteristics: The demographic data of the 40 patients included in this are presented in **Table 1** were 22 patients were female (55%) and 18 patients were male gender (45%) with no statistical difference were found between study groups in respect to both genders. The mean age of the study groups was as follows: control group (42.5 ± 5) years, group 1 (48.6 ± 7.1) years, and group 2 patients were (49.3 ± 6.6) years. The BMI value of control subjects were (26.7 ± 0.8) kg/m^2, while in the patient groups were (29.2 ± 1.9**)** kg/m^2 in group 1, and (29.2 ± 1.6) kg/m^2 with and group 2 with. The statistical difference was found between patient groups and control subjects ($P<0.001$).

TABLE 1: PATIENTS DEMOGRAPHIC CHARACTERISTIC

Variables		Study groups			Total
		Control n %	Group 1 n %	Group 2 n %	n %
Gender	Female	6 42.9%	8 61.5%	8 61.5%	22 55.0%
	Male	8 57.1%	5 38.5%	5 38.5%	18 45.0%
Total		14	13	13	40
p value			0.526 NS		

Variables	Control	Group 1	Group 2	*P* value
Age (years)	42.5 ± 5	48.6 ± 7.1	49.3 ± 6.6	0.013*
BMI (kg/m^2)	26.7 ± 0.8	29.2 ± 1.9	29.2 ± 1.6	<0.001**

Data presented as mean ± SD, and number (n) and percentage (%) were:
NS: Not significant (p>0.05), * Significant difference (p<0.05), ** Highly Significant difference (p<0.001)

2. Changes in Oxidation and Inflammation Markers in Type 2 Diabetic Patients Treated for Three Months: In the present study, there was significant elevation in baseline level of both serum MDA and TNF- α in patient groups 1 and 2 compared to control subjects, with statistically high

difference was found between patient groups and control subjects (*P*<0.001). Also, a highly significant reduction in serum MDA and TNF- α level after 3 months of treatment was found in group 2 patients only compared to pretreatment level (*P*<0.001), but no significant reduction was found in group 1 patients compared to pretreatment level (p>0.05) **(Table 2).**

The serum hs-CRP in both patient groups 1 and 2 was statistically high compared to control subjects (*P*<0.001), and highly significant reduction in serum hs-CRP level after 3 months of treatment was found in both patients groups compared to pretreatment level (*P*<0.001), with no significant difference between patient groups.

TABLE 2: OXIDATION AND INFLAMMATION MARKERS IN TYPE 2 DIABETIC PATIENTS TREATED FOR THREE MONTHS

Variables	Study groups	Pretreatment	Post-treatment	*P* value
MDA nmol/ml	Control	5.73 ± 1.52	.	
	Group 1	10.53 ± 0.72 [a**]	9.92 ± 0.63	0.128[NS]
	Group 2	10.51 ± 0.8 [a** bNS]	8.81 ± 1.1 [b*]	<0.001**
hs-CRP **ng/l**	Control	2.64 ± 0.76	.	
	Group 1	4.66 ± 0.73 [a**]	4.02 ± 0.67	0.017*
	Group 2	4.63 ± 0.63 [a** bNS]	3.96 ± 0.53 [bNS]	0.014*
TNF- α ng/ml	Control	120.37 ± 21.95	.	
	Group 1	275.29 ± 62.18 [a**]	245.59 ± 55.75	0.185[NS]
	Group 2	264.79 ± 65.14 [a** bNS]	200.59 ± 67.13 [b*]	0.005*

Data presented as mean ± SD were: a. Comparison with the control group. B. Comparison with group 1
NS: Not significant (p>0.05), * Significant difference (p<0.05), ** Highly Significant difference (p<0.001)

Hyperglycemia may induce oxidative stress and the possible mechanisms for inducing such stress are well documented, as mentioned earlier.

Fortunately, in the present study, the addition of evening primrose oil to metformin in newly diagnosed T2DM patients produce significant reduction (p<0.05) in serum MDA concentration in comparison with patients treated with metformin alone, which means that evening primrose oil may have a promising antioxidant effect in these patients.

This result is compatible with that of DE La Cruz *et al* where the addition of evening primrose oil to the normolipemic and hyperlipemia rabbits decrease the level of serum MDA that mean reduce the lipid peroxide production and enhance the antioxidant activity of glutathione [15].

Recently and experimentally, El-Sayed *et al.* in his study found restoration of joint activity and antioxidant status by daily treatment of evening primrose oil with aspirin or celecoxib produced a significant reduction in serum MDA levels compared to aspirin or celecoxib alone [16]. Another recent study on the use as the antioxidant of a mixture of α-lipoic acid and evening primrose oil has evidenced an improvement in neuropathic pain through increased PGE1 synthesis [17].

Despite the potent anti-inflammatory effect of metformin, the present study found that adding evening primrose oil to metformin produce a significant reduction in TNF-α concentration (p<0.05) in comparison with patients treated with metformin alone, a promising anti-inflammatory effect of the Gamma-Linolenic acid (GLA) in .

This result is compatible with the previous study observed anti-inflammatory and anti-angiogenic activities which are confirmed by histopathological findings and revealed that EPO significantly reduced the synovial hyperplasia and inflammatory cells invasion in joint tissues since gamma-linolenic acid can suppress inflammatory cytokines level in human blood lymphocytes [16]. Manal *et al.*, found that the addition of EPO to arthritic rats produce a significant reduction in IL-4 and TNF-α levels [18].

The effect of EPO rich in omega-6 essential fatty acids (EFAs) particularly (GLA) which have anti-inflammatory properties [19]. Previous studies have reported that the therapeutic anti-inflammatory effects of EPO may be due to the direct action of its component EFAs on immune cells, as well as their indirect effect on the synthesis of eicosanoids such as prostaglandins, cytokines and cytokine mediators [20].

In a retrospective study that there was a strong and graded association of serum hs-CRP level with the incidence of diabetes independent of established risk factors [21]. Similar significant elevation in the level of the serum hs-CRP was found in the present study T2DM patients compared to control subjects. But the addition of evening primrose oil to metformin showed a slight but nonsignificant reduction in serum hs-CRP concentration in comparison with patients on metformin alone.

Previous results also showed no significant effect of the addition of GLA (the essential ingredient in the EPO) on CRP formation [22]. Belch *et al.,* also confirmed that the addition of EPO to the patients with rheumatoid arthritis did not produce a significant effect on CRP level [23].

The patients are overweight, and the role of adipose tissues in metabolic dysfunctions has long been considered but their potential role in inflammatory processes is a new expanding concept, because this issue is an important metabolically active endocrine organ that secretes various hormones and cytokines, known as adipokines [24], that targets several tissues and cell types, and one of its major actions is to control hepatic production of inflammatory proteins such as CRP, which is an important cardiovascular risk factor [25]. Accordingly, all these findings can explain the non-significant differences between patient groups and a different percent of the reduction in this parameter after 3 months.

3. Blood Pressure Changes in Type 2 Diabetic Patients Treated for Three Months: There were statistically significant elevations in the baseline level of systolic and diastolic B. Pin both patient groups 1 and 2 compared to control subjects ($P< 0.05$). Also, a significant reduction in B.P level after 3 months of treatment was found in group 2 patients only compared to pretreatment level ($P< 0.01$), but no significant reduction was found in group 1 patients compared to pretreatment level ($p>0.05$) **Table 3**.

TABLE 3: BLOOD PRESSURE CHANGES IN TYPE 2 DIABETIC PATIENTS TREATED FOR THREE MONTHS

Variable	Study groups	Pretreatment	Post-treatment	*P* value
Systolic mmHg	Control	127.86 ± 6.99	.	
	Group 1	134.62 ± 6.6 [a*]	136.15 ± 5.06	0.531[NS]
	Group 2	134.62 ± 6.6 [a* bNS]	128.46 ± 5.55[b*]	<0.01*
Diastolic mmHg	Control	82.14 ± 4.26	.	
	Group 1	85.38 ± 5.19 [a*]	86.92 ± 4.8	0.422[NS]
	Group 2	84.62 ± 5.19 [a NS bNS]	83.08 ± 4.8 [b*]	<0.01*

Data presented as mean ± SD were: a. Comparison with the control group. B. Comparison with group 1
NS: Not significant ($p>0.05$), * Significant difference ($p<0.05$), ** Highly Significant difference ($p<0.001$).

Increase in the systolic blood pressure and diastolic blood pressure is the major risk for macrovascular complications in T2DM. In the present study, the combination of evening primrose oil and metformin significantly reduce both systolic blood pressure and diastolic blood pressure compared to metformin alone ($p<0.05$).

This effect is due to the vasodilator effect of GLA founded in EPO that when converted in the body to prostaglandin E1, which possess anti-inflammatory, antiplatelet, and vasodilating properties [26].

This result is also compatible with the previously mentioned study where supplementation with EPO in patients with impaired glucose tolerance show a significant lowering of both systolic and diastolic blood pressure [27]. Another study done by Catherine *et al.* (2013) confirmed a significant difference in systolic and diastolic blood pressure between users and non-users of this dietary supplements [28].

CONCLUSION: Up to our knowledge, we are aware of no randomized controlled trial that assessed the effect EPO administration on metabolic and inflammatory markers in type 2 diabetic patients, particularly among the Iraqi population. And the significant reduction in serum MDA and TNF-α levels after three months of combining evening primrose oil supplement to the conventional metformin therapy at the onset of diagnosis gives no doubt that GLA plays a pivotal role in the disease process, and the dietary control of fatty acid intake would be expected to modify the disease progression.

It can be concluded that early intervention with natural oil rich in gamma-linolenic acid, which possesses anti-angiogenic, anti-inflammatory, and anti-oxidant activities, with traditional hypoglycemic drugs can improve therapeutic benefits and represent a promising strategy to restrain the progression of diabetes complications.

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CONFLICT OF INTEREST: Nil

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