Exploration of Foods and Foodomics

Open Exploration

Open Access Review

Olive oil, fruit and leaves in diabetes mellitus type 2 treatment

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Academic Editor: Marcello Iriti, Milan State University, Italy
Received: August 22, 2023 **Accepted:** October 12, 2023 **Published:** October 29, 2023

Cite this article: Nosić M, Waisundara VY, Banjari I. Olive oil, fruit and leaves in diabetes mellitus type 2 treatment. Explor Foods Foodomics. 2023;1:192–205. https://doi.org/10.37349/eff.2023.00015

Abstract

The Mediterranean dietary pattern, where extra virgin olive oil (EVOO) takes the central spot, is related to longer life expectancy and lower risk of a number of non-communicable diseases, including cardiovascular, diabetes, dementias, and cancer. Positive effect of olive oil on a broad spectrum of diseases, including diabetes mellitus type 2 (DMT2), is usually attributed to its fatty acid content (e.g., oleic acid). Yet, in the last two decades researchers confirmed that, the phenolic compounds (e.g., oleuropein) also significantly alter on glycaemic regulation. Other unprocessed parts of olive plant (fruit and leaves) showed positive impact on glycaemic variability among individuals living with DMT2. The present review focuses on the available research findings on the effect of olive oil, fruits, and leaves on DMT2 treatment. Specifically, the focus is on polyphenols and fats of olive oil, fruits, and leaves with regard to their antidiabetic biological activities.

Keywords

Diabetes mellitus type 2, olive oil, olive fruit, olive leaves, fatty acids, polyphenols

Introduction

Diabetes mellitus is a group of metabolic disorders related to altered metabolism of glucose, protein and lypids which, if untreated, due to hyperglycaemia (elevated glucose concentration in the blood) cause a number of acute and chronic complications. Hyperglycaemia can be a consequence of an absolute or a relative lack of the insuline, insuline resistance, increased glucose formation and of excessive impact of hormones with opposite effects from the insulin on all other organs. The main reason for metabolic abnormalities lies in insufficient effect of insulin on the targeting tissues. There are several patological processes involved in the development of diabetes mellitus, ranging from autoimmune destruction of the pancreatic β-cells with a consequence of apsolute or relative insulin shortage [type 1; diabetes mellitus type

1 (DMT1)] to abnormalities related to insulin resistance (type 2; DMT2). DMT1 affects around 5–10% of individuals while the remaining 90–95% individuals have DMT2 [1].

DMT1 is an autoimmune disease which is a consequence of extraordinary apoptosis of pancreatic β-cells. On the other hand, DMT2 is not an autoimmune disease and has a strong correlation with poor eating habits and excessive consumption of nutritionally low-quality foods (e.g., soft drinks, fast food, candies). Thus, fat and carbohydrate intake are crucial in the development of DMT2 [2].

High-energy daily intake combined with lack of physical activity leads to the development of DMT2. Orientation to a healthy lifestyle is essential for prevention of DMT2 as well as for deterring the development of diabetic complications. Intensive life-style changes are far more effective compared to treatment with oral anti-diabetic treatment regimens such as metformin, and are in correlation with a significant improvement of blood glucose concentration, blood pressure, and blood lipids. If nutritional therapy goals are not achieved in the time period from 3 months to 6 months, it is necessary to introduce pharmacological therapy with the oral anti-diabetic treatments [3, 4]. It has been observed that some integral chemical compounds (e.g., fatty acids, polyphenols) of olive fruit, olive oil, and olive leaves have the ability to lower blood glucose concentrations among persons living with DMT2 and consequently can be very useful in nutritional treatment of DMT2 in a raw form or in the form of various products [5].

Important role in DMT2 pathology has adipokines adiponectin and leptin; their ratio is considered as insulin resistance predictor. When tumor necrosis factor (TNF)-α production of intracellular reactive oxygen species (ROS) is inhibited, adiponectin cannot be suppressed because new amounts of ROS are not produced. TNF-α causes inflammation because it activates transcription factors [e.g., nuclear factor-kappa B (NF-κβ)]. Adiponektin inhibits TNF-α and interleukin (IL) 6. After binding on its cell receptors, adiponektin activates adenosine mono phosphate (AMP)-kinase in the liver and muscles and fatty acid oxidation is increased and triglyceride concentration in the tissue is decreased. Opposite, low concentration of leptin in the bloodstream stimulates food intake [6].

Pancreatic β-cells are extremely sensitive to elevated glucose concentration in the blood stream. Insulin production is decreased because of the chronically elevated glucose concentration which cause β-cell apoptosis. Elevated blood glucose also initiates ROS production through electron transport chain (ETC) and NADPH oxidase. NADPH oxidase could be activated through advanced glycation end products (AGEs) which are common in blood of diabetics. In diabetics ETC is very active which also cause massive deliberation of ROS in the blood stream. In the presence of free fatty acids, ROS was produced and it also reflected on β-cell dysfunction [7].

Olive oil

Secondary metabolites of olive oil are divided into following categories: aroma compounds, hydrocarbons, sterols, tocopherol and phenols. The most abundant tocopherol in olive oil is α-tocopherol, while β- and γ-tocopherols are found in traces. The content of α-tocopherol in olive oil is influenced by cultivation conditions, olive's degree of ripeness, storage conditions, and time. Aroma compounds (e.g., hexanal, 2,4-decadienal, 3-carene) are products of oxidative degradation of unsaturated fatty acids. Aliphatic and aromatic hydrocarbons, alcohols, ketons, ethers, and esters are also included in the specific smell and taste of olive oil. Squalen is the most important hydrocarbon in olive oil. It's a triterpen and intermedier on cholesterol biosynthesis. Besides squalens, olive oil also contains other hydrocarbons [e.g., provitamin A (β-carotene) and lutein] [8].

The most important phytoterol found in olive oil is β-sitosterol which represents 75–90% of total sterols in the olive oil. Campesterol (less than 4%) and stigmasterol (less than 2%), while Δ^5-avenasterol can be found at concentrations between 5% and 20%. Few studies showed a positive impact of β-sitosterol on blood glucose concentration in diabetics [9, 10].

Fatty acids

There are many fatty acids found in olive oil, but oleic acid (55% to 83%), palmitic acid (7.5% to 20%), and linoleic acid (3.5% to 21%) are found in the highest concentrations. Other fatty acids found in olive oil,

listed in decreasing order are linolenic acid, stearic acid, palmitoleic acid, arachidonic acid, eicosenoic acid, heptadecanoic acid, behenic acid, lignoceric acid, and myristic acid [11–13].

The majority of health benefits attributed to olive oil come from its mono-unsaturated fatty acids (MUFAs; e.g., oleic acid). The Mediterranean diet, abundant in oleic acid (C18:1), in comparison to a diet abundant in linoleic acid, reduces the risk for developing DMT2 and atherosclerosis [14–17]. MUFAs are far more effective in decreasing postprandial glucose level in comparison to poly-unsaturated fatty acids (PUFAs) [18].

Linoleic acid (C18:2) can be found in olive oil in a concentration range from 3.5% to 21% and linoleic acid present in olive oil is present in ≤ 1.0%. The ratio between those two fatty acids should be 5:1 in order to perform eicosanoids (i.e., leukotrienes, lipoxins) synthesis. Eicosanoids are substances similar to hormones and they are usually derived from arachidonic acid [19]. Eicosanoids can be used as markers for predicting the early risk of DMT2 in general [20]. Eicosanoids (e.g., prostaglandins) derived from arachidonic acid have proinflammatory and vasoconstrictive properties, while those derived from eicosapentanoic acid (e.g., leukotrienes) have a weak proinflammatory and vasoconstrictive properties [19]. Eicosanoids are able to prolong the presence of glucose-transporters in the plasma membrane [19, 21]. A high proportion of linoleic acid in foodstuffs in cholesterol esters and in phospholipids can lower the incidence of diabetes [22]. Its concentration correlates significantly with fasting glucose (FG), therefore, it is suggested to substitute animal fats with plant fats [23], and olive oil is often emphasized as the best source of vegetable fats. This change in the contribution of fats from particular food sources can reduce the risk for developing diabetes [24]. When a diet rich in linoleic acid (e.g., sunflower oil) is compared to a diet abundant in oleic acid (e.g., olive oil), FG is lower on a diet rich in oleic acid as compared to linoleic acid diet. Additionally, a diet rich in linoleic acid increases the concentration of low-density lipoprotein (LDL)-cholesterol [16]. Oleic acid protects mitochondria from oxidative stress caused by palmitic acid because it reduces the level of ROS [25]. Extra virgin olive oil (EVOO) regulates postprandial glucose concentration through incretin [e.g., glucagon-like peptide-1 (GLP-1)] excretion and their binding on β-cell receptors [26].

Additionally, insulin resistance in DMT2 is mediated through adipokines and TNF-α, which is produced in fatty tissue and immune system. Hormone adiponectin functions as TNF-α-antagonist and is well known for its insulin-sensitizing properties in the liver and muscles. Adiponectin activates adenosine mono phosphate-activated protein kinase (AMPK) which stimulates oxidative degradation of glucose and fatty acids [27]. Olive oil compounds, namely oleic acid and hydroxytyrosol (HT) individually showed successful results in preventing of adiponectin decrease by itself or in combination. Those effects were better when oleic acid and HT were combined, particularly when they originated from olive oil-incorporating dietary patterns, which is the case in the Mediterranean diet [28].

Phenolic compounds

Polyphenols (phenolic compounds) are secondary plant metabolites and one of the most abundant in the plant world. There are one or more hydroxyl groups directly attached to one or more aromatic hydrocarbons in their structure. The whole group is named according to their fundamental representative phenol. There are over 8,000 structural variants of phenolic compounds and they can be categorized in the two main groups: flavonoids and non-flavonoids. Flavonoids are one of the most explored among polyphenols with almost 9,000 different flavonoids identified to date. They are divided into various subgroups [flavonols, flavons, isoflavons, flavan-3-ols, flavanons, and anthocyans (including anthocyanidins)]. Representatives of flavonols are quercetin, myricetin, kaempferol, morin, galangin and their glycosides (rutin and astragalin). Their aglycons are not present in plants. Luteolin, apigenin, baikalein, krisin and their glycosydes are considered to be in the group of flavons. Also, naringenin, hesperetin, eriodictol and their glycosides (naringin, hesperidin, liquiritin) are considered to belong to this group of flavonols. Flavan-3-ols are found as simple monomers (e.g., catechins, epigallocatechins, gallocatechins) to complex polymers (proantocyanidins). Antocyans are the major group of flavonoids which have over 600 different compounds. Aglycons of anthocyans are named antocyanidins and in the

natural enviroment occur as: pelargonidin, cyanidin, delphinidin, petunidin, and malvidin. Antocyans can be acylated with various hydroxycinnamic acids (e.g., caffeic, *p*-coumaric, ferulic) and alyphatic acids (e.g., acetic, malic, oxalic). There are two subgroups considered in the group of non-flavonoids: derivatives of hydroxybensoic acid (e.g., vanillic, gallic, *m*-hydroxybensoic) and derivatives of hydroxycinnamic acid (e.g., *p*-coumaric acid, ferullic acid, caffeic acid, sinapic and chlorogenic acid) [29–31].

Compared to purified olive oil, EVOO concentration of phenolic compounds is four times higher [32]. Polyphenols from olive oil reduce mitochondrial ROS and therefore, are very useful in the diabetes treatment. Polyphenols from olive leaves have the same effects. Polyphenols encourage the transfer of insulin-regulated glucose transporter-4 (GLUT4) into muscle tissue [33]. EVOO contains higher amounts of squalenes and their components (e.g., oleuropein, tocopherol) compared to purified olive oil [34]. There is an inversed correlation observed between polyphenol intake and FG concentration because they reduce synthesis of AGEs [e.g., hemoglobin A1c (HbA_1c)] [35]. Squalenes could have been transformed into cholesterol in the metabolism, but it is not the case because of the excretion in the stool even if daily consumption is high (e.g., 1 g/day). Olive oil phenolic compounds decrease the concentration of proinflammatory molecules (e.g., leucotrienes) [36]. EVOO contains a mixture of polyphenols with one or two hydroxyl groups. After digestion olive oil, polyphenols are bind to LDL-particles and prevent their oxidation [37, 38]. With the consumption of olive oil on a one-time basis, there is a maximal concentration of tyrosol and HT in plasma 2 h after consumption [39, 40].

Individuals diagnosed with metabolic syndrome (MS) often develop DMT2 as a result of insulin resistance. Therefore, it is stated that MS predicts DMT2 and that individuals living with MS are five times more likely to develop DMT2 [41–43]. Virgin olive oil (VOO) polyphenols have a positive influence on MS and consequently on DMT2 [44]. Except oleic acid, certain polyphenols present in olive oil also have favourable effects on human health [45, 46]. Suitable daily intake of polyphenols is positively correlated with the decrease od DMT2 [47–51]. In several early research, health benefits of olive oil were attributed just to MUFAs (oleic acid) but after it a numerous bioactive compounds were taken into consideration (e.g., oleuropein, caffeic acid, HT, and luteolin) [52–54]. EVOO, based on its oleuropein content, reduces postprandial blood glucose concentration [55, 56]. Daily consumption of 20 mL of EVOO increased the concentration of GLP-1 [57, 58]. An increased concentration of GLP-1 consequently decreases the level of ROS [59]. Exenatide was the first GLP-1 receptor agonist (RA) used in DMT2 treatment [60]. GLP-1 is a gastrointestinal incretin hormone which concentration is very low in the period of fasting and increases after food consumption especially after glucose intake [57, 61]. EVOO is able to increase insulin sensitivity, and reduces dipeptidyl peptidase-4 activity which consequently elevates GLP-1 [62, 63]. The daily intake of EVOO and diabetes mellitus are in an opposite correlation [64]. Adults suffering from cardiovascular diseases (CVDs) had a 40% significantly decreased risk of DMT2 in the 4 years period of intake [65]. Individuals consuming olive oil have significantly decreased the risk of developing DMT2 compared to those consuming sunflower oil [66]. Oleuropein is present in much greater concentration in EVOO compared to ordinary olive oil. This phenolic compound has postprandial glucose lowering properties [67, 68]. Individuals living with DMT2 were treated with polyphenol-free olive oil during four weeks and after that with EVOO abundant on polyphenols. All patients were overweight. EVOO had a significant correlation with the decrease of FG as well as with the decrease of HbA_1c. There were only 11 patients in this particular study [64, 69]. Oleuropein is able to inhibit GLUT2 transporters [70–73]. Research done on 25 individuals living with DMT2 showed a decrease of postprandial glucose concentration in the blood. In this research, ordinary chocolate was compared to chocolate combined with EVOO. Polyphenol oleuropein from olive oil has a notable relevance in lowering postprandial glucose level and it is of great interest regarding the glycaemic control [74]. Oleuropein, HT and tyrosol are hydrolytic degradation products [54]. HT is very stable in alimentary tract and has high bioaccessibility in the organism. HT, tyrosol, and their derivatives build up to 90% of total polyphenols in olive oil [75]. VOO which is used in the Mediterranean diet regulates glucose concentration in the blood and consequently the occurrence of DMT2 [76]. For each increase of 10

g/day of olive oil there is a 9% decrease of DMT2 development, but there is no effect in daily intake above 15 g [69]. Research on EVOO showed a significant correlation between glucose concentration and HbA_1c concentration in the blood after 56 days of EVOO daily intake. Adipokines (visfatin and apelin) have possible effects on glucose metabolism. Visfatin is elevated among individuals living with DMT2. EVOO showed decreasing properties in modification of visfatin concentration in the blood [64]. That consequently leads to a decrease of HbA_1c concentration in the blood which is crucial because 1% increase of HbA_1c concentration causes 28% increase of general mortality [77]. The Mediterranean diet, supplemented with EVOO, decreases glucose concentration in the blood [78]. DMT2 and the MS are in significant correlation because individuals suffering from MS are in great probability to develop DMT2 [79, 80]. Among 13 individuals living with MS, the consumption of EVOO decreased blood glucose concentration [81].

Positive effect of EVOO on lowering blood glucose is related to postprandial increase of GLP-1 and a decrease of lipopolysaccharide (LPS). Because of changes in the gut permeability, low-grade endotoxemia (LGE) is consequently decreased. LGE is a consequence of tight junction (TJ) proteins modifications. TJ proteins are modified when concentrations of LPS and zonulin are decreased which enhances gut permeability [62, 82, 83]. One research including 1,282 individuals living with DMT2 showed that the Mediterranean diet supplemented with EVOO is able to prevent retinopathy [84]. Oleuropein and HT can inhibit glucose transporter 2 [85].

Olive fruit

Olive fruit contains 15–35% of olive oil [86]. Chemical components in table olives are presented in Table 1. Olive fruit contains vitamins soluble in water (C, B_1, B_2, B_5, B_6, B_9) as well as vitamins soluble in fat (A and E). Olive fruit contain minerals: magnesium, calcium, iron, and potassium. Phenolic compounds tyrosol and HT are also present in olive leaves. Tyrosol and HT are categorised as phenolic alcohols and are among the main compounds which can be found in olive fruit. HT with elenolic acid forms secoiridoid compound oleuropein is specific for the family Oleaceae [87]. Oleuropein is also found in leaves in 3,000 higher concentration. Oleuropein reduces glucose concentration in the blood as well as lipid concentration. Oleuropein is also a component of EVOO [70]. Obese men who received oleuropein capsules (51 mg/day) showed a significant improvement in β-cell functioning and post-prandial glucose concentration [88]. In another conducted research, oleuropein in capsules (35–200 mg/day), decreased the concentration of blood glucose after sucrose intake [71]. Subjects who consumed oleuropein supplements had lower postprandial glucose concentration in comparison to those who were given no supplements [89]. Even patients who consumed oleuropein enriched chocolate (with EVOO) had a lower postprandial glucose level in comparison to patients who ate no oleuropein enriched chocolate [74]. Oleuropein 60-day treatment (100 mg/day) decreases blood glucose in diabetics [71]. Oleuropein has an impact on gut microbiota and consequently on DMT2. That property also has HT from olive leaves [90]. Phenolic compounds are abundant in olive fruit tissue and are mostly soluble in water. They can also be found in olive oil but in very low concentration. Concentration of phenolic compounds depends on the degree of ripeness of the fruit. Levels of luteolin, tyrosol, and HT increase with olive fruit's degree of ripeness. HT inhibits the occurrence of pro-inflammatory leukotriene B4. Polyphenols are able to inhibit carbohydrate absorption and consequently postprandial glucose concentration in the blood [91]. When vitamin E is consumed in natural occurring foodstuffs (e.g., natural olive oil), compared to supplements, its effects are much better (or symbiotic) because of the presence of various secondary metabolites [92]. Although the olive fruit has a low concentration of proteins (1–3%), their nutritional value is very important. That is because of the content of essential amino acids (e.g., leucine, isoleucine, lysine) [93]. Dietary fibre components in olive fruit are mainly pectin, hemicellulose, and cellulose. Pectin is classified as water soluble dietary fibre, cellulose as water insoluble dietary fibre and hemicellulose as partially soluble dietary fibre [94]. Soluble dietary fibres, because of their viscosity, increase intestinal transit time and in that way can decrease glucose concentration in the blood. Postprandial glucose lowering effect cannot be observed with consumption of water insoluble dietary fibre [95, 96].

Table 1. Chemical composition of the olive fruit [86]

Component	%
MUFAs	60–80
Water	50–70
Saturated fatty acids	12–20
Fat	18–35
Total sugar	18
Reducing sugar	2–6
PUFAs	5–18
Minerals	1–5
Potassium	0.5–3.4
Dietary fiber	1–3
Proteins	1–3
Cellulose	1.5–2
Hydrocarbons	0.8–1
Polyphenols	0.5–0.8
Tocopherols	0.3–0.8
Phosphorous	0.02–0.25
Calcium	0.02–0.20
Sodium	0.01–0.20
Sulphur	0.01–0.13

Olive leaves

Olive leaf extracts (OLEs) lower postprandial glucose concentration in the blood. Olive leaves have another impact on human organism compared to olive oil. The positive effects of olive leaves are mainly attributed to the following compounds: oleuropein, oleanolic acid, oleacein, erythrodiol, tyrosol, HT; oleuropein obtained from OLEs regulates glucose concentration in the blood because it affects insulin receptor substrates (IRSs), especially IRS1 and IRS2. After phosphorylation, those substrates activate serine/threonine kinase protein kinase B (Akt/PKB) and stimulate glucose entrance in the cells [97]. In a study conducted with olive leaf tea, the results on healthy individuals showed a significant decrease of blood glucose concentration related with decreased time of starch degradation due to α-amylase inhibition [98]. Oleuropein inhibits differentiation of adipocytes. In a clinical trial among 41 patients (27 men and 14 women) those who drank olive leaves tea for 14 weeks had a much lower concentration of HbA_1c compared to those not drinking olive leaf tea at all [97]. The usage of 500 mg OLE for 7 days significantly decreased HbA_1c concentration in DMT2 patients [99]. Oleanolic acid is also very important triterpenoid present in olive leaves and has antidiabetic properties. It inhibits α-glucosidase. Isomer of oleanolic acid is ursolic acid (UA). Oleanolic acid and UA are able to inhibit gluconeogenesis in the liver. Oleanolic acid derivative bardoxolone methyl showed a positive impact on DMT2 patients suffering from chronic kidney disease (CKD) [99].

Suggestions for further research

Most studies reviewed here were *in vitro* and animal studies. However, the potential of various components of olive oil, fruits, and/or leaves is evident and more randomized clinical trials on human subjects are needed. Available findings of various olive plant products in patients with DMT2 or MS are summerized in Table 2. It is especially important to conduct human studies which will be able to determine whether the observed beneficial effect of olive oil is specific only to its consumption or is it rather the combined effect in the Mediterranean diet [100]. Surely, lifestyle, from physical activity [101] to sleep patterns and psychological condition [102] can alter blood glucose, therefore well designed studies are needed to examine the role of olive oil on gylcaemia. Also, the potential of olive oil on some types of cancer shed a new light on its health benefits [103].

Table 2. Overview of human studies involving various olive plant products

Product of olive plant	Food component concentration	Treatment (duration, number of participants, gender, age)	Effect/main outcome	Reference
EVOO	10 g EVOO in meal	Postprandial blood sample was collected at 1:00 PM (before lunch), and 60 min and 120 min after lunch (proteins: 16–19%; carbohydrates: 53–54%; fats: 28–30%) 30 IFG patients Gender: 17 males and 13 females Age: 58.1 years ± 11.4 years	20% decrease of blood glucose and insulin Δ change 18 mg/dL	[48]
EVOO	EVOO, 25mL/day (577 mg phenolic compound/kg) ROO, 25 mL/day (polyphenols not detectable)	11 overweight DMT2 patients First four weeks "wash out" period—only ROO. Remaining four weeks EVOO (high in polyphenols) Gender: 7 men and 4 postmenopausal women Age: 64.63 years ± 8.52 years	EVOO significantly reduced fasting plasma glucose (P = 0.023), HbA_1c (P = 0.039), BMI (P = 0.012), and body weight (P = 0.012)	[55]
Oleuropein enriched chocolate	40 g oleuropein eriched chocolate and Mediterranean eating pattern (long before and during clinical trial)	25 DMT2 patients (compared to 20 healthy patients; 10 males/10 females; age: 33.9 years ± 6.9 years) Gender: 12 males and 13 females Age: 69 years ±8 years After washout period (10 days) participants took oleuropein non-enriched chocolate	Administration of 40 g oleuropein enriched chocolate is associated with modest or no increase of glycaemia DMT2 patients and healthy subjects	[65]
EVOO	10 mL/day at lunch and dinner	13 patients suffering from MS Gender: 5 males and 8 females Age: 51.9 years ± 7.4 years Measures was conducted at the beginning and after 90 days	After 90 days of the study blood glucose decreased from average 93 mg/dL to average 86.0 mg/dL	[72]
Capsules with OLE	Period of 12 weeks Single dose (4 capsules) contains 51.1 g oleuropein and 9.7 mg HT	45 overweight patients Gender: only men Age: 46.4 years ± 5.5 years Participants received 4 capsules with OLEs as a single dose 12 weeks once a day	After 12 weeks supplementation insulin sensitivity was significantly improved compared to placebo group (P = 0.009)	[79]
Capsules with olive leaf and fruit extracts	Period of 2 months Single dose (2 capsules) contains 100 mg/day oleuropein and 20 mg/day HT	663 patients suffering from hypertension—134 prediabetic and 44 diabetic Gender: 327 males and 336 female Age: 60 years ± 12 years 2 months supplementation	After 2 months supplementation FG was significantly improved (with a decrease of 4.8%), P < 0.0001	[62]
Capsule with OLE	Period of 14 weeks Single dose (1 capsule) contains 500 mg OLE	41 patient suffering from DMT2 Gender: 27 males and 14 females Age: 18–79 years 14 weeks supplementation	After 14 weeks supplementation HbA_1c was significantly lower (compared to placebo group)	[88]

BMI: body mass index; IFG: impaired fasting glucose; P: the level of statistical significance; ROO: refined olive oil

Conclusions

Olive oil, especially extra virgin, was found to be effective for glycaemic control in individuals with DMT2. These benefits are primarily attributed to fatty acid and phenolic composition of olive oil. Still, the majority of these findings, especially in terms of lower DMT2 risk in olive oil consumers come from observational (cohort) studies focused on the Mediterranean diet as a whole. Therefore, more randomized clinical trials are needed to elucidate which components of olive oil expose the strongest effect on glycaemia control. Other parts of olive, both fruits and leaves (consumed as a tea) were found to have the same beneficial

effect on hyperglycaemia, but there is insufficient number of human studies to provide conclusive evidence. More studies are needed, especially human studies, which will not only strengthen current recommendations to include olive oil in daily diet, but potentially lead to the development of new pharmacological solutions (especially in regard to exploiting olive leaves) to aid public health crisis of diabetes the world is facing.

Abbreviations

DMT2: diabetes mellitus type 2

EVOO: extra virgin olive oil

FG: fasting glucose

GLP-1: glucagon-like peptide-1

HbA1c: hemoglobin A1c

HT: hydroxytyrosol

IRSs: insulin receptor substrates

MS: metabolic syndrome

MUFAs: mono-unsaturated fatty acids

OLEs: olive leaf extracts

ROS: reactive oxygen species

TNF: tumor necrosis factor

Declarations

Author contributions

MN: Data curation, Writing—original draft. VYW: Validation, Writing—review & editing. IB: Conceptualization, Validation, Writing—review & editing. All authors read and approved the final version of the manuscript.

Conflicts of interest

No potential conflicts of interest were reported by the authors.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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