J Biochem Tech (2020) 11 (2): 41-45
ISSN: 0974-2328

# Evidence that supports the antidiabetic, antihypertensive, and antihyperlipidemic effects of olive (*Olea europaea* L.) leaves extract and its active constituents (oleuropein) in human

**Heba A. Sindi**

Received: 03 December 2019 / Received in revised form: 10 April 2020, Accepted: 19 April 2020, Published online: 15 May 2020


## Abstract

The Kingdom of Saudi Arabia is one of the countries in the Middle East burdened with type 2 diabetes (T2D). This type of diabetes is associated with an increase in the body's resistance to insulin action. Elevated blood pressure is one of the most important diseases that accompany T2D. Many experimental and clinical studies have shown the effectiveness of olive leaves extract (OLEx) in controlling T2D, as well as hypertension. This review aimed to collect clinical studies conducted in humans that prove the effectiveness of OLEx or its active constituent (*oleuropein*) in combating T2D, hypertension, and hypolipidemia. Several studies conducted in humans (diseased and healthy) showed the effectiveness of OLEx or oleuropein in reducing both blood glucose and lipids. It also improved the vascular functions and reduced inflammation associated with high blood pressure and diabetes. The mechanisms behind these pharmacological activities were to scavenge free radicals, increase insulin production, and reduce its resistance, raise nitric oxide synthesis, and dilate blood vessels. From toxicological studies in experimental animals, it has been shown that the OLEx may be safe to use. In conclusion, studies on humans showed the effectiveness of OLEx in managing T2D, hyperlipidemia, and hypertension, but there were limited-number trials and did not use large numbers of participants, and therefore large studies must be conducted to document effectiveness and safety of OLEx.

**Key words:** Olive leaves extract, Type 2 diabetes, Hypertensive, Dislipidemia

## Introduction

Diabetes mellitus is one of the most common health problems faced by mankind and is a major public health problem (Najafipour *et al.*, 2018; Adiga and Kathyayan, 2019; Sheikhi *et al.,* 2019). Type 2 diabetes (T2D) is one of the chronic diseases endemic in the world. The T2D is widespread among millions of people on the globe, and Saudi Arabia is one of the countries with the highest prevalence of the disease (Naeem, 2015; Kolb and Martin, 2017). The Kingdom of Saudi Arabia ranks second in the Middle East and seventh in the world in containing diabetes (Abdulaziz Al Dawish *et al*., 2016). The occurrence of this type of diabetes is due to one and/or both of the two main reasons: insufficient insulin secretion and/or the body's resistance to insulin action which causes chronic blood glucose rise (Siddiqui *et al*., 2013). Prolonged high blood sugar causes a state of oxidative stress due to the accumulation of free radicals and the consumption of antioxidants. Oxidative stress is the main cause of various and serious complications of T2D (Matough *et al*., 2012).

There are many regimens and medicinal systems that are used effectively to control T2D. But all of them failed to fully control the level of blood glucose, and then many of its users suffer from various diabetes complications. These medicines also have many side effects and are costly that burden the patients. This prompted specialists and patients to search for therapeutic alternatives from herbs and medicinal plants for use in T2D treatment systems (Ota and Ulrih, 2017; Annunziata, 2018). In recent times, the goal of many researchers was to reveal the therapeutic efficacy and the mechanism of action of many herbs and nutritional supplements for use as therapeutic adjunctive to control T2D in a real reflection of the desire of patients as well as the pharmacy market (Annunziata, 2018).

High blood pressure is one of the most important causes of vascular disease, cardiac disorders, and high mortality rates (Huang *et al*., 2019). Essential hypertension is closely related to endocrine and metabolic disorders (Kasacka *et al*., 2015). Scientists also reported that an increase in insulin levels and related factors (as in T2D) is a direct cause of hypertension in humans (Wang *et al*., 2017).

Olive (*Olea europaea* L.) trees are one of the most important agricultural products in the Mediterranean basin (Peralbo-Molina and Luque deCastro, 2013). Olive leaves have long been used in medication for diabetes as one of the popular folk treatments (Komaki *et al*., 2003). It is common to use olive leaf extract (OLEx) as well as its tea in Mediterranean and European countries (Abaza *et al*., 2015). The OLEx is distinguished by its high antioxidant value compared to other parts of the plant (Lins *et al*., 2018). Besides this, OLEx contains many biologically active substances including phenolic compounds, which have many therapeutic activities like antidiabetic, antihyperlipidemic, antihypertensive, antimicrobial, and antioxidant effects (Lockyer *et al*., 2012; Guinda *et al*., 2015; Soliman *et al*., 2019). Oleuropein is the phenolic compound most commonly found in olive leaf, and it gives the bitter taste of virgin and edible oil (Cifá *et al*., 2018).

While there are many studies of the potential therapeutic effect of OLEx, few have been done on humans. This study aimed to collect

**Heba A. Sindi**

Department of Food and Nutrition, Faculty of Human Sciences and Design, KAU, Jeddah, Saudi Arabia.

the clinical trials that have proven the therapeutic effect of olive leaves, OLEx, and/or oleuropein on T2D and/or its various complications.

*Antidiabetic effect of olive (Olea europaea L.) leaves extract*

In a study that aimed to investigate the effect of taking OLEx tablets (500 mg/day) for 14 weeks on glucose homeostasis in adults with T2D, the trial was done on 79 outpatient clinic diabetics. The study showed the ability of the OLEx to reduce the level of hemoglobin A1c (HbA1c) and fasting insulin level compared to the control group (Wainstein *et al*., 2012). Besides, in a controlled double-blinded clinical study conducted on 46 middle-aged participants of overweight (BMI 25–30 kg/m $^2$) men (more susceptible to future metabolic syndrome and T2D). They were given capsules containing OLEx for 3 months. The results of the study indicated a significant improvement in the tissue sensitivity towards insulin, as well as a statistically significant increase in the ability of the pancreas to secrete insulin (de Bock *et al*., 2013).

Another study aimed to know the effect of extra virgin olive oil on the level of blood glucose and lipids in patients with impaired fasting blood glucose. The study was conducted on 30 patients who were divided to eat either a meal containing 10 g of the oil or a meal free of it. The study showed an improvement in postprandial blood sugar and fat in these patients after they consumed the oil (Carnevale *et al*., 2017). A recent study aimed to research the effect of consuming oleuropein on blood glucose concentration after two hours of meals. The study was conducted on 20 healthy subjects who were placed in two groups, one of whom took 20 mg of oleuropein and the other was the placebo. The measurements resulted in a noticeable decrease in the level of glucose and dipeptidyl-peptidase-4 (DPP-4) in the blood, and a statistically significant increase in insulin and glucagon-like peptide-1 compared to the placebo group (Carnevale *et al*., 2018).

In addition, a recent study aimed to compare the effect of oleuropein-enriched chocolate and control chocolate on blood glucose and insulin levels in patients with T2D and healthy subjects. Twenty-five diabetics of type 2 and 20 healthy subjects were collected to participate in this study. Participants consumed 40 g of oleuropein-enriched chocolate or control chocolate. The study showed that oleuropein-enriched chocolate resulted in a moderate rise or no change in the state of glycemia in T2D patients and healthy people, respectively (Del Ben *et al*., 2019).

*Antidiabetic mechanisms of olive (Olea europaea L.) leaves extract*

Several experimental studies suggested that the most important mechanism by which the ethanolic OLEx reduces blood glucose is to increase the peripheral uptake of glucose (Al-Azzawie and Alhamdani, 2006; Yaseen Khan *et al*., 2007). It was described that OLEx may raise glucagon-like peptide-1 excretion *in vivo* and *in vitro* experiments and consequently can be applied as adjunctive therapy in T2D (Rafferty *et al*., 2011).

A systematic review of several laboratory studies conducted on experimental rats showed that OLEx increases insulin secretion from the beta cells of the Langerhans islands (Abunab *et al*., 2017). Carnevale *et al*. (2018) demonstrated that the hypoglycaemic effect of oleuropein is *via* lowering the signs of oxidative stress which included soluble NADPH oxidase-derived peptide activity, 8-iso-prostaglandin-2α, and platelet p47$^{phox}$ phosphorylation) that were analyzed two hours after the meal. A recent study showed that oleuropein control T2D is likely to be mediated through incretin modulation (Del Ben *et al*., 2019).

*Hyperlipidemia and hypertension effects of olive (Olea europaea L.) leaves extract*

In a study carried out on 40 patients with borderline hypertension, it was found that the administration of OLEx in a dose of 1000 mg four times a day for 12 weeks significantly decreased the patient's blood pressure, total cholesterol, and LDL (Perrinjaquet-Moccetti *et al*., 2008). In a longitudinal, randomized study, compared to control which conducted on 39 patients with high blood lipids (male and female), it was found that adding 1200 mg of OLEx daily to patients resulted in significant decreases in the total cholesterol, low-density lipoprotein, triglycerides, and ratio of total cholesterol/high-density lipoprotein (Fonollá *et al*., 2010).

Another study was conducted on 148 patients (male and female) in the first stage of high blood pressure. Patients were supplied with 1000 mg of OLEx every day. While the control group was supplied with Captopril (antihypertensive drug). The treatment lasted for two months. The study revealed that consuming OLEx reduced blood pressure (both systolic and diastolic) and also lowered blood lipid levels compared to the Captopril group (Susalit *et al*., 2011).

More recently, a study was aimed to verify the effect of OLEx on the function of the vascular system, as well as signs of inflammation that occur postprandial. The study was conducted on 18 male and female volunteers who consumed 51 mg of oleuropein for one time only. The results of the study showed a marked decrease in digital volume pulse stiffness index (a measure of vascular function) as well as the level of the inflammatory cytokine as interleukin 8 compared to the control group (Lockyer *et al*., 2015)

A cross-over controlled clinical study was conducted on 60 male subjects aged 45 ± 12.7 years in the pre-hypertensive stage (systolic blood pressure: 121-140 mmHg; diastolic blood pressure: 81-90 mmHg). They were eligible to consume polyphenol-rich OLEx (136 mg) for 6 weeks. A marked decrease in systolic and diastolic blood pressure was observed throughout the day, and the 24-hour measure compared to the control group. The results also indicated significant decreases in total cholesterol, low-density lipoprotein, as well as triglycerides in comparison with the control group (Lockyer *et al*., 2017).

In addition to the effect of OLEx as to lower blood pressure, a recent study showed that the extract can reduce inflammation and hypertension complications on the liver and kidneys. A

randomized study was conducted on 60 hypertensive patients (30-60 years). The participants were divided into two groups, one of them consumed the OLEx and the other represented the control group. The study lasted for 3 months. It was found that consuming OLEx tablets reduced the inflammatory factors associated with hypertension, while the renal and liver functions did not change as a result of consuming the OLEx in these patients (Javadi *et al*., 2019).

*Antihypertensive/anti-hyperlipidaemic mechanisms of olive (Olea europaea L.) leaves extract*

The study conducted to examine the effect of OLEx on T2D animals accompanied by renal hypertension induced by streptozotocin (STZ), nicotinamide, and closure of the renal artery. The results showed that there was a drop in systolic blood pressure. Researchers attributed this to the antioxidant effect of OLEx. The extract also increased nitric oxide concentration which induced beneficial vasodilator effect (Nekooeian *et al*., 2014a).

It was also noted in another study that the oleuropein has caused the protection of the cardiovascular system in the T2D accompanied by high blood pressure due to impaired kidney function. The underlined mechanism was confirmed to be due to the inhibition of the action of the angiotensin-converting enzyme, the closure of calcium channels, the widening of blood vessels, the restoration of endothelial function, as well as the antioxidant effect, and the scavenging of oxygen free radicals (Jemai *et al*., 2009; Rodriguez-Rodriguez *et al*., 2009; Nekooeian *et al*., 2014b).

In a study on mice fed on meals with high fat content, it was found that treating mice with OLEx had reduced the blood lipid levels (total cholesterol, LDL, and triglyceride), and the authors explained this to the enhanced effect of the antioxidant enzymes (catalase (CAT) and superoxide dismutase (SOD)) that were measured in liver tissue (Jemai *et al*., 2008).

*Safety of olive (Olea europaea L.) leaves extract*

Due to the many therapeutic uses of OLEx, it was necessary to determine the extent of its safe use. Many studies indicated that using the OLEx even in high doses did not have any toxic symptoms (Clewell *et al*., 2016; Guex *et al*., 2018). Acute toxicity studies (2000 mg/kg) and sub-chronic toxicity (100-400 mg/kg for 4 weeks) showed no toxicity symptoms when using OLEx (Guex *et al*., 2018). The chronic toxicity of the OLEx (360-1000 mg/kg/day for 3 months) did not result in any toxic symptoms or deaths (Clewell *et al*., 2016). On the contrary, a previous study reported some histopathological changes and bleeding in the liver and kidneys of rats treated with OLEx 0.9 % for 6 weeks (Omer *et al*., 2012). Upon review of the publication, there was insufficient information on the genetic toxicity of the OLEx (Acar-Tek and Ağagündüz, 2020).

## Conclusion

From the collected studies it could be concluded that OLEx effectively controls T2D, dyslipidemia, and hypertension. However, there were restricted-number of studies that were carried on human and thus it is recommended that huge studies must be organized to record the potential therapeutic activity as well as the safety of OLEx.

## References

Abaza, L., Taamalli, A., Nsir, H., & Zarrouk, M., (2015). Olive tree (Olea europeae L.) leaves: Importance and advances in the analysis of phenolic compounds. *Antioxidants. 4*(4):682-98. https://doi.org/10.3390/antiox4040682

Abdulaziz Al Dawish, M., Alwin Robert, A., Braham, R., Abdallah Al Hayek, A., Al Saeed, A., Ahmed Ahmed, R., & Sulaiman Al Sabaan, F., (2016). Diabetes Mellitus in Saudi Arabia: A Review of the Recent Literature. Curr. Diabetes Rev. 12, 359–368. https://doi.org/10.2174/1573399811666150724095130

Abunab, H., Dator, W.L., & Hawamdeh, S., (2017). Effect of olive leaf extract on glucose levels in diabetes-induced rats: A systematic review and meta-analysis. *J. Diabetes 9*, 947–957. https://doi.org/10.1111/1753-0407.12508

Acar-Tek, N., & Ağagündüz, D., (2020). Olive Leaf (Olea europaea L. folium): Potential Effects on Glycemia and Lipidemia. Ann. Nutr. Metab. 2020: 1-6. https://doi.org/10.1159/000505508.

Adiga, U. & Kathyayani, P. (2019). Association of Insulin Resistance with Liver Biomarkers in Type 2 Diabetes Mellitus. *International Journal of Pharmaceutical and Phytopharmacological Research*, 9 (1), 88-91.

Al-Azzawie, H.F., & Alhamdani, M.S.S., (2006). Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. *Life Sci.* 78, 1371–1377. https://doi.org/10.1016/j.lfs.2005.07.029

Annunziata, G., (2018). Oleuropein as a novel anti-diabetic nutraceutical. An overview. *Arch. Diabetes Obes*. 1, 54–58. https://doi.org/10.32474/ado.2018.01.000113

Carnevale, R., Loffredo, L., Del Ben, M., Angelico, F., Nocella, C., Petruccioli, A., Bartimoccia, S., Monticolo, R., Cava, E., & Violi, F., (2017). Extra virgin olive oil improves post-prandial glycemic and lipid profile in patients with impaired fasting glucose. *Clin. Nutr.* 36, 782–787. https://doi.org/10.1016/j.clnu.2016.05.016

Carnevale, R., Silvestri, R., Loffredo, L., Novo, M., Cammisotto, V., Castellani, V., Bartimoccia, S., Nocella, C., & Violi, F., (2018). Oleuropein, a component of extra virgin olive oil, lowers postprandial glycaemia in healthy subjects. *Br. J. Clin. Pharmacol.* 84, 1566–1574. https://doi.org/10.1111/bcp.13589

Cifá, D., Skrt, M., Pittia, P., Di Mattia, C., & Poklar Ulrih, N., (2018). Enhanced yield of oleuropein from olive leaves using ultrasound-assisted extraction. *Food Sci. Nutr.* 6, 1128–1137. https://doi.org/10.1002/fsn3.654

Clewell, A.E., Béres, E., Vértesi, A., Glávits, R., Hirka, G., Endres, J.R., Murbach, T.S., & Szakonyiné, I.P., (2016). A

Comprehensive Toxicological Safety Assessment of an Extract of Olea Europaea L. Leaves (Bonolive™). *Int. J. Toxicol.* 35, 208–221. https://doi.org/10.1177/1091581815619764

de Bock, M., Derraik, J.G.B., Brennan, C.M., Biggs, J.B., Morgan, P.E., Hodgkinson, S.C., Hofman, P.L., & Cutfield, W.S., (2013). Olive (Olea europaea L.) Leaf Polyphenols Improve Insulin Sensitivity in Middle-Aged Overweight Men: A Randomized, Placebo-Controlled, Crossover Trial. *PLoS One 8*(3):e57622. https://doi.org/10.1371/journal.pone.0057622

Del Ben, M., Nocella, C., Loffredo, L., Bartimoccia, S., Cammisotto, V., Mancinella, M., Angelico, F., Valenti, V., Cavarretta, E., Carnevale, R., & Violi, F., (2019). Oleuropein-enriched chocolate by extra virgin olive oil blunts hyperglycaemia in diabetic patients: Results from a one-time 2-hour post-prandial cross over study. *Clin. Nutr*. https://doi.org/10.1016/j.clnu.2019.09.006

Fonollá, J., Díaz-Ropero, P., de la Fuente, E., & Quintela, J.C., (2010). Ms358 one-month consumption of an olive leaf extract enhances cardiovascular status in hypercholesterolemic subjects. Atheroscler. *Suppl.* 11, 182. https://doi.org/10.1016/s1567-5688(10)70859-x

Guex, C.G., Reginato, F.Z., Figueredo, K.C., da Silva, A.R.H. da, Pires, F.B., Jesus, R. da S., Lhamas, C.L., Lopes, G.H.H., & Bauermann, L. de F., (2018). Safety assessment of ethanolic extract of Olea europaea L. leaves after acute and subacute administration to Wistar rats. *Regul. Toxicol. Pharmacol*. 95, 395–399. https://doi.org/10.1016/j.yrtph.2018.04.013

Guinda, Á., Castellano, J.M., Santos-Lozano, J.M., Delgado-Hervás, T., Gutiérrez-Adánez, P., & Rada, M., (2015). Determination of major bioactive compounds from olive leaf. LWT - Food Sci. *Technol.* 64, 431–438. https://doi.org/10.1016/j.lwt.2015.05.001

Huang, Yonglian, Chen, Y., Cai, H., Chen, D., He, X., Li, Z., Cai, X., Peng, X., Huang, Yaxiu, Li, S., Cao, Q., Wang, P., & Chen, B., (2019). Herbal medicine (Zhengan Xifeng Decoction) for essential hypertension protocol for a systematic review and meta-analysis. *Med. (United States)* 98, e14292. https://doi.org/10.1097/MD.0000000000014292

Javadi, H., Yaghoobzadeh, H., Esfahani, Z., Memarzadeh, M.R., & Mirhashemi, S.M., (2019). Effects of olive leaf extract on metabolic response, liver and kidney functions and inflammatory biomarkers in hypertensive patients. *Pakistan J. Biol. Sci.* 22, 342–348. https://doi.org/10.3923/pjbs.2019.342.348

Jemai, H., Bouaziz, M., Fki, I., El Feki, A., & Sayadi, S., (2008). Hypolipidimic and antioxidant activities of oleuropein and its hydrolysis derivative-rich extracts from Chemlali olive leaves. *Chem. Biol. Interact.* 176, 88–98. https://doi.org/10.1016/j.cbi.2008.08.014

Jemai, H., Feki, A.E.L., & Sayadi, S., (2009). Antidiabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats. *J. Agric. Food Chem*. 57, 8798–8804. https://doi.org/10.1021/jf901280r

Kasacka, I., Janiuk, I., & Piotrowska, Z., (2015). Evaluation of CART-, glucagon-, and insulinimmunoreactive cells in the pancreas of an experimental rat model of unilateral renal artery stenosis. *Histol. Histopathol.* 30, 445–452. https://doi.org/10.14670/HH-30.445

Kolb, H., & Martin, S., (2017). Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. *BMC Med. 15*(1): 131. https://doi.org/10.1186/s12916-017-0901-x

Komaki, E., Yamaguchi, S., Maru, I., Kinoshita, M., Kakehi, K., Ohta, Y., & Tsukada, Y., (2003). Identification of Anti-.ALPHA.-Amylase Components from Olive Leaf Extracts. *Food Sci. Technol. Res.* 9, 35–39. https://doi.org/10.3136/fstr.9.35

Lins, P.G., Marina Piccoli Pugine, S., Scatolini, A.M., & de Melo, M.P., (2018). In vitro antioxidant activity of olive leaf extract (Olea europaea L.) and its protective effect on oxidative damage in human erythrocytes. *Heliyon 4*(9):e00805. https://doi.org/10.1016/j.heliyon.2018.e00805

Lockyer, S., Corona, G., Yaqoob, P., Spencer, J.P.E., & Rowland, I., (2015). Secoiridoids delivered as olive leaf extract induce acute improvements in human vascular function and reduction of an inflammatory cytokine: A randomised, double-blind, placebo-controlled, cross-over trial. *Br. J. Nutr.* 114, 75–83. https://doi.org/10.1017/S0007114515001269

Lockyer, S., Rowland, I., Spencer, J.P.E., Yaqoob, P., & Stonehouse, W., (2017). Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial. *Eur. J. Nutr.* 56, 1421–1432. https://doi.org/10.1007/s00394-016-1188-y

Lockyer, S., Yaqoob, P., Spencer, J.P.E., & Rowland, I., (2012). Olive leaf phenolics and cardiovascular risk reduction: Physiological effects and mechanisms of action. *Nutr. Aging* 1, 125–140. https://doi.org/10.3233/NUA-2012-0011

Matough, F.A., Budin, S.B., Hamid, Z.A., Alwahaibi, N., & Mohamed, J., (2012). The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ. *Med. J. 12*(1): 5. https://doi.org/10.12816/0003082

Naeem, Z., (2015). Burden of Diabetes Mellitus in Saudi Arabia. *Int. J. Health Sci. (Qassim).* 9, V–VI. https://doi.org/10.12816/0024690.

Najafipour, M., Bani Mohammad, M., Zareizadeh, M. & Najafipour, F. (2018). Step by step in management of type 2 diabetes. *International Journal of Pharmaceutical and Phytopharmacological Research*, 8(5), 68-71.

Nekooeian, A., Khalili, A., & Khosravi, M., (2014a). Oleuropein offers cardioprotection in rats with simultaneous type 2 diabetes and renal hypertension. *Indian J. Pharmacol.* 46, 398–403. https://doi.org/10.4103/0253-7613.135951

Nekooeian, A.A., Khalili, A., & Khosravi, M.B., (2014b). Effects of oleuropein in rats with simultaneous type 2 diabetes and renal hypertension: A study of antihypertensive mechanisms. *J. Asian Nat. Prod. Res.* 16, 953–962. https://doi.org/10.1080/10286020.2014.924510

Omer, S.A., Elobeid, M.A., Elamin, M.H., Hassan, Z.K., Virk, P., Daghestani, M.H., Al-Olayan, E.M., Al-Eisa, N.A., & Almarhoon, Z.M., (2012). Toxicity of olive leaves (Olea europaea L.) in Wistar albino rats. *Asian J. Anim. Vet. Adv.* 7, 1175–1182. https://doi.org/10.3923/ajava.2012.1175.1182

Ota, A., & Ulrih, N.P., (20170. An overview of herbal products and secondary metabolites used for management of type two diabetes. *Front. Pharmacol.* 8:436. https://doi.org/10.3389/fphar.2017.00436

Peralbo-Molina, Á., & Luque deCastro, M.D., (2013). Potential of residues from the Mediterranean agriculture and agrifood industry. *Trends Food Sci. Technol. 32*(1):16-24. https://doi.org/10.1016/j.tifs.2013.03.007

Perrinjaquet-Moccetti, T., Busjahn, A., Schmidlin, C., Schmidt, A., Bradl, B., & Aydogan, C., (2008). Food supplementation with an olive (Olea europaea L.) leaf extract reduces blood pressure in borderline hypertensive monozygotic twins. *Phyther. Res.* 22, 1239–1242. https://doi.org/10.1002/ptr.2455

Rafferty, E.P., Wylie, A.R., Elliott, C.T., Chevallier, O.P., Grieve, D.J., & Green, B.D., (2011). In vitro and in vivo effects of natural putative secretagogues of Glucagon-like peptide-1 (GLP-1). *Sci. Pharm.* 79, 615–621. https://doi.org/10.3797/scipharm.1104-16

Rodriguez-Rodriguez, R., Herrera, M.D., De Sotomayor, M.A., & Ruiz-Gutierrez, V., (2009). Effects of pomace olive oil-enriched diets on endothelial function of small mesenteric arteries from spontaneously hypertensive rats. *Br. J. Nutr.* 102, 1435–1444. https://doi.org/10.1017/S0007114509990754

Sheikhi, H. R., Heydari, M. A., Soleimani, M., Sheikhi, A. R., Mastaelizadeh, H. & Naderyanfar, F. (2019). The effect of family-centered education on self-care rate in patients with type 2 diabetes. *Journal of Advanced Pharmacy Education & Research*, 9(S2), 89-93.

Siddiqui, A.A., Siddiqui, S.A., Suhail, A., Siddiqui, S., Ahsan, I., & Sahu, K., (2013). Diabetes: Mechanism, Pathophysiology and Management-A Review | Insight Medical Publishing. *Int. J. Drug Dev. Res.* 5, 1–23.

Soliman, G.A., Saeedan, A.S., Abdel-Rahman, R.F., Ogaly, H.A., Abd-Elsalam, R.M., & Abdel-Kader, M.S., (2019). Olive leaves extract attenuates type II diabetes mellitus-induced testicular damage in rats: Molecular and biochemical study. *Saudi Pharm. J.* 27, 326–340. https://doi.org/10.1016/j.jsps.2018.11.015

Susalit, E., Agus, N., Effendi, I., Tjandrawinata, R.R., Nofiarny, D., Perrinjaquet-Moccetti, T., & Verbruggen, M., (2011). Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: Comparison with Captopril. *Phytomedicine* 18, 251–258. https://doi.org/10.1016/j.phymed.2010.08.016

Wainstein, J., Ganz, T., Boaz, M., Bar Dayan, Y., Dolev, E., Kerem, Z., & Madar, Z., (2012). Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats. *J. Med. Food* 15, 605–610. https://doi.org/10.1089/jmf.2011.0243

Wang, F., Han, L., & Hu, D., (2017). Fasting insulin, insulin resistance and risk of hypertension in the general population: A meta-analysis. *Clin. Chim. Acta.* 464:57-63. https://doi.org/10.1016/j.cca.2016.11.009

Yaseen Khan, M., Panchal, S., Vyas Yashvantrai, N., Butani, A., & Kumar, V., (2007). Olea europaea: A Phyto-Pharmacological Review. *Pharmacogn. Rev.* 1, 114–118.