

## Review Article

# Therapeutics role of olive fruits/oil in the prevention of diseases via modulation of anti-oxidant, anti-tumour and genetic activity

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**Abstract:** The current mode of treatment for various diseases is based on synthetic drugs are effective but they show adverse effect and also alter the genetic and metabolic activity. Moreover, some drugs prepared from plants and their constituents show potentiality with more efficacy than synthetic agents used in clinical therapy. Earlier report has shown that regular consumption of fruits and vegetables is strongly related with reduced risk of developing various diseases. Several epidemiological studies has shown that, the incidence heart disease and cancers is lowest in the Mediterranean basin as compared to the part of the world because of their diet rich in olives and olive products. Olives are commonly consumed in Mediterranean and Arabian Peninsula and also have been documented in Holy Quran and modern scientific literatures. Earlier studies have shown that, the constituents from olive such as oleuropein, squalene and hydroxytyrosol modulate the genes functions and other activities. In this review, the medicinal value of olives and their constituents are summarized in terms of therapeutic approach in the diseases management through regulation of various activities.

**Keywords:** Olive, antioxidant activity, anti-tumour activity, diseases control

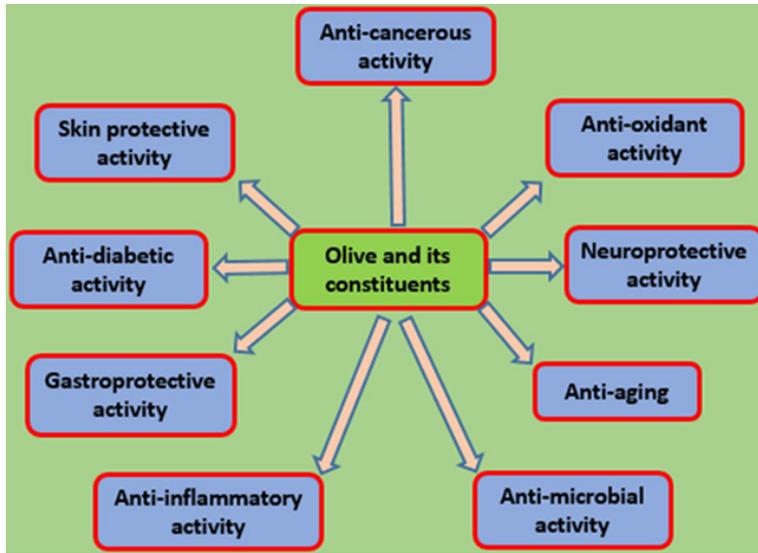
## Introduction

Medicinal plants and their constituents used to cure the diseases development and progression since ancient time. Turmeric, *Nigella sativa* and dates fruits show a role in the management of diseases via antioxidant, anti-inflammatory and other various activities such as modulation of genetic pathways [1-6]. Current mode of treatment based on synthetic drugs is effective but also shows side effect. Chemotherapy and radiotherapy are effective treatment modality used to manage the malignancies but also shows severe toxicity in tissues. Safe and effective drugs are needed to control the diseases development and progression. Natural products are good substitute in the prevention of cancer through modulation of cellular and molecular activities without any complications. Plants and their products are in used to treat the diseases since ancient time and also has important place in Ayurveda and Unani medicine.

In Islam, herbs and its constituents has important value in diet and treatment of various diseases. The Prophet Mohammed (PBUH) used various herbs e.g. dates, black seed, olive and recommended various medicinal plants for cure of diseases [7, 8].

The olive tree, *Olea europaea*, produces the olive fruit and is one of the vital components of Mediterranean diet. Oleic acid, a monounsaturated fatty acid plays an important role in cancer prevention, while squalene showed anticancer effects. Several epidemiological studies has shown that, the incidence of coronary heart disease (CHD) and cancers is lowest in the Mediterranean basin as compared to the part of the world because their diets are rich in olives and olive products [9].

Olive and their constituents show a vital role in diseases management via antioxidant, anti-tumour and anti-microbial and modulation of gene functions (**Figure 1**).



**Figure 1.** Olive and their constituents show a vital role in the diseases management.

### Antioxidant activity

The oxidation process is one of the major culprits in the cell membrane damage, lipid and DNA damage in our body. Natural defence system as antioxidant present in our body that neutralizes the products created by oxidation viz free radical. Imbalance in defence system and oxidation processes creates a free radical accumulation and causes diseases development and progression. Plants and their constituents are safe and effective remedy in the control of diseases via antioxidant activity. Cancer chemoprevention via antioxidant approaches offer key strategy for inhibiting, delaying, or even reversing the process of carcinogenesis [10, 11]. Various plant and their constituents such as turmeric, black seed, dates and ginger play a major role in control of diseases via antioxidant activity. Phenol compounds play a role in trapping the free radicals directly or scavenge them via a series of coupled reactions with antioxidant enzymes [12]. Olive fruits, oil and leaves play a vital role in the management of various diseases due to the presence of simple phenol (hydroxytyrosol, tyrosol), polyphenols (oleuropein glucoside); and other constituents secoiridoids (SID), the dialdehydic form of oleuropein (SID-1). Earlier investigators have shown that *in vitro* and *ex vivo* models; olive oil phenolic have shown to have antioxidant properties, higher than that of vitamin E, on lipids and DNA oxidation [13-16].

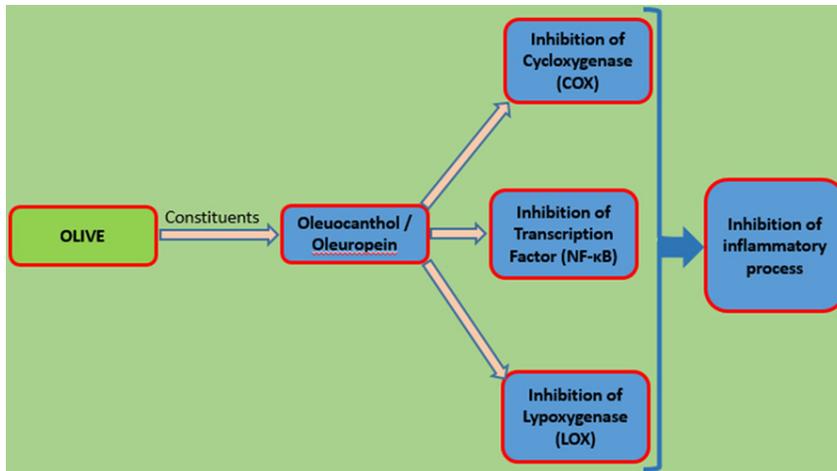
### Anti-microbial activity

Drug resistance incidence is increasing worldwide and also acts as blocker in treatment outcome. Bacterial resistance against various antimicrobial agents is one of the main culprits in treatment failure. The treatment based on antibiotics against bacteria or micro-organism, which causes other complications. Natural products in the form of olive and their constituents are good therapeutic approach in the management of infectious diseases and also they are economical, capable of devoid of side effects. Earlier reports based on *in-vitro* and *in-vivo* studies have shown that olive

leaf, seed extract shows a vital role in the inhibition of bacterial activity.

An important study based on olive leaf activity against bacteria such as *Campylobacter jejuni*, *Helicobacter pylori* and methicillin-resistant *Staphylococcus aureus* (MRSA) showed antimicrobial activity.

Other report in the support of olive leaf extract act as antimicrobial where all tested bacteria were killed within three hours with the dose/concentration of 0.6% (w/v) water extract but Dermatophytes were inhibited via other dose with 1.25% (w/v) plant extract a 3-day exposure [17]. An important finding showed that Virgin olive oil as protective effect against foodborne pathogens and olive oil also reduced the count of inoculated *Salmonella enteritidis* and *Listeria monocytogenes* by approximately 3 log CFU/g in salad and mannose [18]. *Helicobacter pylori* is a main culprit in the stomach cancer and also responsible for gastric cancer [19]. An interesting study showed the antimicrobial activity of olive oil against the Gram-negative bacteria *Helicobacter pylori* [20]. Another study reported that, different constituents of olive play a significant role as inhibitory effect or slowdown the growth of various types of bacteria and fungi [21]. In the support of olive as antimicrobial has shown that, olive hydroxytyrosol might be considered as a promising antimicrobial agent for treating human infections [22]. Olive



**Figure 2.** Olive and their constituents show a significant effect in regulation of inflammatory process via modulation of genes.

oil vegetation water act as toxic for both phytopathogenic *Pseudomonas syringae* (Gram-negative) and *Corynebacterium michiganense* (Gram-positive) bacteria [23]. Olive and their constituents play a role against virus and US patent declare that Oleuropein contains a powerful antiviral activities against some virus such as herpes mononucleosis, hepatitis virus, rotavirus, bovine rhinovirus, canine parvovirus, and feline leukemia virus [24]. Another studies also reported that, oleuropein has vital antiviral activity against virus including respiratory syncytial virus and para influenza type 3 viruses [25].

#### Anti-inflammatory activity

Anti-inflammatory products are a substance has ability to reduce inflammation. Anti-inflammatory drugs make up about half of analgesic, remedying pain by reducing inflammation, which affect the central nervous system and also cause other complications. Currently non steroidal anti-inflammatory drugs are commonly used to treat the inflammation but this drug shows an adverse side effect. Olive is a safe, inexpensive substitute in the reduction of inflammation and maintain or regulate the genes involve in this process. The mechanism by which Olive seed/leaf exerts have anti-inflammatory action appears to be through inhibiting cyclooxygenase and lipoxygenase (Figure 2). Earlier studies have proven that, olive and their constituents have anti-inflammatory property. An important reports in the support of olive as anti-inflammatory reported

that, Oleocanthal, phenolic compound of virgin olive oil shows similar anti-inflammatory properties to ibuprofen [26].

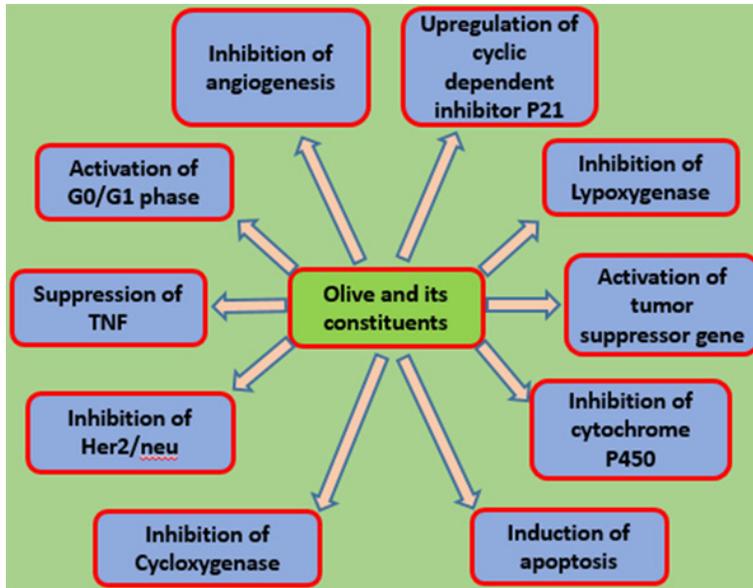
COX-1 and COX-2 convert arachidonic acid to prostaglandin, resulting in pain and inflammation. None steroidal anti-inflammatory drugs, commonly prescribed to treat arthritis, work by inhibiting prostaglandins. NSAIDs, however, also cause gastrointestinal problems including

ulcers. Phenolic compounds oleocanthal, an inhibitor of the COX-1 and COX-2 enzymes, possesses similar potency as the NSAID ibuprofen. Another enzyme play a vital role in inflammation is lipoxygenase. The constituents oleocanthal is not very effective in the control of lipoxygenase but others constituents shows a role in the inhibition of lipoxygenase. A report has shown that, oleuropein elicits anti-inflammatory effects by inhibiting lipoxygenase activity and the production of leukotriene B<sub>4</sub> [27]. Another supportive evidence of Olive leaf extract functions as anti-inflammatory properties and inhibition of platelet aggregation and thromboxane A<sub>2</sub> production [28, 29]. Nuclear factor kappa is a vital component in inflammation and also play role in pathogenesis of various diseases. Numerous medicinal plants play a role as anti-inflammatory and control the various diseases development and progression via inhibition of NF-κB and COX2. An interesting study demonstrated that, curcumin showed as anticancer, antioxidant and anti-inflammatory effects via the down-regulation of the transcription factors NF-κB, AP-1 and Egr-1 [30]. Black seed also shows an anti-inflammatory effect. Earlier report showed that mechanism of action via inhibition of TNF-α gene expression and NO synthases [31] and provides the down modulation of various cytokines and chemokines [32].

#### Anti-cancerous activity

Cancer is a multi-factorial diseases and major health problem worldwide. Various factors responsible for the development of cancers are

## Olive in the prevention of various diseases



**Figure 3.** Olive and their constituents play a role in cancer prevention via modulation of genes.

smoking, chewing, dye, bacteria and HIV. Carcinogens show a vital effect in the cancer development via alteration of tumour suppressor gene, apoptotic genes and DNA repair enzymes. The current mode of treatment based on radiotherapy, chemotherapy and synthetic drugs are effective but also show adverse effect. Various medicinal plants and their constituents show a significant in the management of cancer. Earlier studies have shown that turmeric and their constituents, *Nigella sativa*, dates fruits shows a role in activation of tumour suppressor gene, induction of apoptotic gene and inactivation of various gene in management of cancer. Several studies has shown that the incidence of coronary heart disease and cancers is lowest in the Mediterranean basin as compared to the part of the world because of the diet with rich in olives and olive products [9]. There are several constituent are in olive and each constituents have a vital role in the prevention of several type of diseases including cancers. Oleic acid, a monounsaturated fatty acid plays an important role in cancer prevention, while squalene showed anticancer effect [33]. Olive oil is rich source of polyphenols and also influential antioxidants and plays a role to promote good health [34] and also shows a role in prevention of cancer. Olive oil shows a role in the prevention of the development of carcinomas and olive oil may have chemopreventive

properties against colon carcinogenesis [35-38]. Earlier researchers have shown that, oleic and linolenic acid showed a proliferation inhibition effect on prostate carcinoma cells [39, 40]. Oleuropein as powerful antioxidant and anti-angiogenic agent and shows a potent anti-tumor agent and cancer-protective effects [41]. Another report has shown that oleuropein showed a role in the inhibition of cell proliferation via slowdown the cell cycle at S phase and up-regulation of cyclin-dependent inhibitor p21 [42].

Olive and their constituents control the cancer development via activation of tumour suppressor gene, induction of apoptotic gene and inactivation of VEGF and oncogene (**Figure 3**).

Tumor suppressor genes such as p53, PTEN and p16 play a vital role in the prevention of tumour growth. p53 is the guardian of all genes, regulate the various cellular and molecular pathways and prevent cancer formation. A study showed that increases p53 gene expression level in MCF-7 cells treated with 100  $\mu$ M oleuropein as compared to untreated cells and cells treated with 200  $\mu$ M oleuropein the expression level was further increased significantly from the untreated cell [43].

Studies support the role of oleuropein and hydroxytyrosol in the prevention of colorectal cancer and showed decrease HIF-1 $\alpha$  protein and upregulation of p53 protein expression [44].

Another key factor such as apoptosis plays a role in this vista. Changes occur in normal process of apoptosis may increase cell survival and promote the development and progression of tumour [45, 46]. Earlier investigators have shown that, medicinal plant may have chemopreventive effects against different type of cancer via the modulation of the expression of the Bcl-2/Bax apoptotic regulatory factors [47]. Dry Olive Leaf Extract promoted cell death mainly via alteration of cell membrane integrity and

late caspase-independent fragmentation of genetic material [48]. An important finding showed that olive oil Hydroxytyrosol acetate affected the transcription of genes involved in apoptosis up-regulating of BNIP3, BNIP3L, PDCD4, and ATF3 and also play a role in activating caspase-3 [49]. A study reported that hydroxytyrosol induces cell cycle arrest and apoptosis *in vitro* and *in vivo* [50].

Angiogenesis is complex process including activation of endothelial cells and proteolytic enzymes in the degradation of the basement membranes and angiogenic factors that play a role in various type of cancer [51-55]. Overexpression of angiogenic factor such as VEGF has been observed in various tumours. Synthetic drugs as anti-angiogenic are effective in tumour treatment but this drug also shows adverse side effects. Olive and their constituents show an important role in the cancer prevention via inactivation of angiogenic process. The phenolic compound oleuropein has antioxidant and anti-angiogenic effect via inhibiting the proliferation and migration of advanced-grade tumor cell lines in a dose-dependent manner [56, 57].

### Anti-diabetic activity

Diabetes mellitus is metabolic disorder and also a major problem in both sexes worldwide. Diabetes mellitus are responsible for renal failure, blindness or diabetic cataract [59] poor metabolic control, and increased risk of cardiovascular disease including atherosclerosis and Advanced Glycation End products [59]. Natural products as medicinal plants and their constituents are good substitute to treat the diabetes and its complication. Ayurvedic and Unani medicine used various plants and their products to treat the diabetes and their complication including diabetic retinopathy. Earlier reports showed that, based on *in-vivo* and *in-vitro* studies olive leaves, seed and oil shows a vital effect in the management of diabetes.

Hypoglycemic activities of olive and their constituents have been observed in various studies. An important reports showed that, hypoglycemic effects of the leaves of *Olea europaea* [60]. The eventual mechanism responsible of the hypoglycemic activity of oleuropein and hydroxytyrosol may result from a potentiating of glucose-induced insulin release or increased

peripheral uptake of glucose [61]. Another findings also shows that oleuropein has role in diabetes via hypolipidemic effects in diabetic rats [62].

Another study has shown that, traditional Arab medicine, with olive leaves, were effective in controlling blood glucose in patients with diabetes [63, 64]. Polyphenols of Olive leaf play a vital role in delaying the progression of advanced glycation end products-mediated inflammatory diseases such as diabetes [65]. A study reported that Olive leaves suppressed the elevation of blood glucose after oral administration of starch in borderline volunteers [66]. Studies have shown that diabetic animals supplemented with olive leaf extracts showed significant reductions in blood sugar and cholesterol [67, 68]. Another report also indicated that when diabetic rats treated with either olive leaf extract or glyburide (Diabeta), showed common glucose-lowering drug [69] and in addition anti-diabetic effects of the extract has shown better results than drug [69].

### Anti-aging effect

Aging is a multi-factorial process that depends on diverse molecular and cellular mechanisms, such as protein availability, genome maintenance and inflammation [70]. Various factors are responsible for aging phenomenon including reactive oxygen species. Olive and their constituents show antioxidant activity and finally play a role in anti-aging process. Earlier studies explore the molecular mechanisms of EVOO by which may influence longevity and this activity are due to the antioxidant potential of its phenolic compounds and free-radical scavengers, such as vitamin E [71]. A report [72] suggesting that tyrosol, a phenol present in EVOO, may increase lifespan and stress resistance in *Caenorhabditis elegans*, via activation of hormonal mechanisms. Other constituents (oleuropein-treated cultures) exhibit a delay or slow-down in the appearance of senescence morphology, and their life span is extended by 15% approximately [73].

### Skin protector

Nutrition plays an important role in the functioning and attractiveness of skin. Dietary supplementation with the deficient vitamins, minerals, or essential fatty acids improves skin

conditions [74]. Natural products contain phenolic compound play a major role to protect the skin from UV light. The constituents of olive such as oleuropein, hydroxytyrosol and squalene show a role in skin protection against UV light and radiation. A study reported that, tropane hydrocarbon (squalene), which shows a role in the filtration of oxygen at skin level [75]. Another report in the support of olive as skin protector has shown that olive especially oleuropein [76] have a direct antioxidant action on skin and also shows free radical scavenger at the skin level. Another supportive report [77] suggested that preventative effects of olive leaf extracts and oleuropein on chronic UVB-induced skin damage.

### Neuroprotector activity

Olive and their constituents show a role in neuroprotector but the exact mechanism behind this is not fully known. It might be due to the phenolic compound present in olive shows neuroprotective effect. Olive oil phenols have various protective role in brain hypoxia-reoxygenation [78, 79] cerebral ischemia [80, 81] brain damage after hypoxia reoxygenation in diabetic rats [82] and ageing [83]. An important study showed that Myelo Peroxidases activity reduced significantly in Olive Extract treated rats when compared with non-treated rats [84]. Another study [85] has reported that, oleuropein decreases or even prevents A $\beta$  aggregation, which is inherent to Alzheimer's disease (AD). Another report showed that OLE-induced ischemic tolerance in rats is partly associated with changes in brain lipids level [86].

### Conclusions

A safe and effective mode of treatment is required to manage the diseases. Some drugs from plants showed potentiality with more efficacy than synthetic agents used in clinical treatment. Earlier report based on experimental model has shown that, regular consumption of fruits and vegetables is strongly associated with reduced risk of developing various diseases. Olive and their constituents with antioxidant, anti-inflammatory and anti-tumour properties create optimism towards the novel therapeutic strategy. In this review, olives and their constituents has medicinal value are summarized in terms of therapeutic approach in the diseases management via anti-oxidant, anti-

microbial, anti-tumour and modulate the various genes normal mechanism of action.

### Disclosure of conflict of interest

None.

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### References

- [1] Aldebasi YH, Aly SM, Rahmani AH. Therapeutic implications of curcumin in the prevention of diabetic retinopathy via modulation of anti-oxidant activity and genetic pathways. *Int J Physiol Pathophysiol Pharmacol* 2013; 5: 194-202.
- [2] Abdelmeguid NE, Fakhoury R, Kamal SM, Al Wafai RJ. Effects of *Nigella sativa* and thymoquinone on biochemical and subcellular changes in pancreatic  $\beta$ -cells of streptozotocin-induced diabetic rats. *J Diabetes* 2010; 2: 256-66.
- [3] Salim EI, Fukushima S. Chemopreventive potential of volatile oil from black cumin (*Nigella Sativa*L.) seeds against rat colon carcinogenesis. *Nutr Cancer* 2003; 45: 195-202.
- [4] Abdu SB. The protective role of Ajwa date against the hepatotoxicity induced by Ochra toxin A. *Egyp J Nat Tox* 2011; 8: 1-15.
- [5] Ragab AR, Elkablawy MA, Sheik BY and Baraka HN. Antioxidant and tissueprotectivestudies on Ajwa extract: dates from Al Madinah Al-Monwarah, SaudiArabia. *J Environ Anal Toxicol* 2013; 3: 2161-0525.
- [6] Ishurd O, Zgheel F, Kermagi A, Flefla M and Elmabruk M. Antitumor activity of beta-D-glucan from Libyan dates. *J Med Food* 2004; 7: 252-255.
- [7] Dar-ul-Iman Healing, 2000. Food of the Prophet (Sallallahu Alayhi Wasallam). Available at: [http://chishti.org/foods\\_of\\_the\\_prophet](http://chishti.org/foods_of_the_prophet).
- [8] Marwat SK, Khan MA, Rehman F, Bhatti IU. "Aromatic Plant Species Mentioned in the Holy Qura'n and Ahadith and Their Ethnomedicinal Importance". *Pakistan Journal of Nutrition* 2009; 8: 1472-1479.
- [9] Keys A. Mediterranean diet and public health: personal reflections. *Am J Clin Nutr* 1995; 61: 1321S-1323S.
- [10] Tsao AS, Kim ES, Hong WK. Chemoprevention of Cancer, CA-A Cancer Journal for Clinicians. *CA Cancer J Clin* 2004; 54: 150-180.
- [11] Shureiqi I, Reddy P, Brenner DE. Chemoprevention: General perspective. *Crit Rev Oncol Hematol* 2000; 33: 157-167.

## Olive in the prevention of various diseases

- [12] Reynolds T, Dweck AC. *Aloe vera* leaf gel, A review update. *J Ethnopharmacol* 1999; 68: 3-37.
- [13] Owen RW, Mier W, Giacosa A, Hule WE, Spiegelhalder B, Bartsch H. Phenolic compounds and squalene in olive oils: the concentration and antioxidant potential of total phenols, simple phenols, secoroids, lignans and squalene. *Food Chem Toxicol* 2000; 38: 647-59.
- [14] Fitó M, Covas MI, Lamuela-Raventós RM, Vilà J, Torrents L, de la Torre C, Marrugat J. Protective effect of olive oil and its phenolic compounds against low density lipoprotein oxidation. *Lipid* 2000; 35: 633-8.
- [15] Masella R, Vari R, D'Archivio M, Di Benedetto R, Matarrese P, Malorni W, Sczzochio B, Giovannini C. Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. *J Nutr* 2004; 134: 785-91.
- [16] De la Puerta R, Ruiz Gutierrez V, Hoult JR. Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem Pharmacol* 1999; 157: 445-9.
- [17] Markin D, Duek L, Berdicevsky I. In vitro antimicrobial activity of olive leaves. *Mycoses* 2003; 46: 132-6.
- [18] Medina E, Romero C, Brenes M, De Castro A. Antimicrobial activity of olive oil, vinegar, and various beverages against foodborne pathogens. *J Food Prot* 2007; 70: 1194-9.
- [19] Romero C, Medina E, Vargas J, Brenes M, de Castro A. In vitro activity of olive oil polyphenols against *Helicobacter pylori*. *J Agric Food Chem* 2007; 55: 680-686.
- [20] Cavallaro L, Egan B, O'Morain C, Di Mario F. Treatment of *Helicobacter pylori* infection. *Helicobacter* 2006; 11: 36-39.
- [21] Bisignano G, Tomaino A, Lo Cascio R, Crisafi G, Uccella N, Saija A. On the in-vitro antimicrobial activity of oleuropein and hydroxytyrosol. *J Pharm Pharmacol* 1999; 51: 971-4.
- [22] Furneri PM, Piperno A, Saija A, Bisignano G. Antimycoplasmal Activity of Hydroxytyrosol. *Antimicrob. Agents Chemother* 2004; 48: 4892-4894.
- [23] Soni MG, Burdock GA, Christian MS, Bitler CM, Crea R. Safety assessment of aqueous olive pulp extract as an antioxidant or antimicrobial agent in foods. *Food Chem Toxicol* 2006; 44: 903-915.
- [24] Fredrickson WR; F and S Group, Inc. Method and Composition for Antiviral Therapy with Olive Leaves. U.S. Patent 2000; 6: 117-884.
- [25] Ma SC, He ZD, Deng XL, But PP, Ooi VE, Xu HX, Lee SH, Lee SF. In vitro evaluation of secoiridoid glucosides from the fruits of *Ligustrum lucidum* as antiviral agents. *Chem Pharm Bull* 2001; 49: 1471-1473.
- [26] Lucas L, Russell A, Keast R. Molecular mechanisms of inflammation. Anti-inflammatory benefits of virgin olive oil and the phenolic compound oleocanthal. *Curr Pharm Des* 2011; 17: 754-68.
- [27] De la Puerta R, Guttierrez VR, Hoult JRS. Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem Pharmacol* 1999; 57: 445-449.
- [28] Pieroni A, Heimler D, Pieters L, van Poel B, Vlietinck AJ. *In vitro* anti-complementary activity of flavonoids from olive (*Olea europaea* L.) leaves. *Pharmazie* 1996; 51: 765-768.
- [29] Petroni A, Blasevich M, Salami M, Papini N, Montedoro GF, Galli C. Inhibition of platelet aggregation and eicosanoid production by phenolic components of olive oil. *Thromb Res* 1995; 78: 151-160.
- [30] Han SS, Keum YS, Seo HJ, Surh YJ. Curcumin suppresses activation of NF- $\kappa$ B and AP-1 induced by phorbol ester in cultured human promyelocytic leukemia cells. *J Biochem Mol Biol* 2002; 31: 337-342.
- [31] Bitler CM, Viale TM, Damaj B, Crea R. Hydrolyzed Olive Vegetation Water in Mice Has Anti-Inflammatory Activity. *J Nutr* 2005; 135: 1475-1479.
- [32] Richard N, Arnold S, Hoeller U, Kilpert C, Wertz K, Schwager J. Hydroxytyrosol Is the Major Anti-Inflammatory Compound in Aqueous Olive Extracts and Impairs Cytokine and Chemokine Production in Macrophages. *Planta Med* 2011; 77: 1890-1897.
- [33] Waterman E, Lockwood B. Active components and clinical applications of olive oil. *Altern Med Rev* 2007; 12: 331-42.
- [34] Wahle KW, Caruso D, Ochoa JJ, Quiles JL. Olive oil and modulation of cell signaling in disease prevention. *Lipids* 2004; 39: 1223-31.
- [35] Gill CI, Boyd A, McDermott E, McCann M, Servili M, Selvaggini R, Taticchi A, Esposto S, Montedoro G, McGlynn H, Rowland I. Potential anti-cancer effects of virgin olive oil phenols on colorectal carcinogenesis models in vitro. *Int J Cancer* 2005; 117: 1-7.
- [36] Bartolí R, Fernández-Bañares F, Navarro E, Castellà E, Mañé J, Alvarez M, Pastor C, Cabré E, Gassull MA. Effect of olive oil on early and late events of colon carcinogenesis in rats: modulation of arachidonic acid metabolism and local prostaglandin E2 synthesis. *Gut* 2000; 46: 191-9.
- [37] Reddy BS, Maeura Y. Tumor promotion by dietary fat in azoxymethane-induced colon carcinogenesis in female F344 rats: influence of amount and source of dietary fat. *J Natl Cancer Ins* 1984; 72: 745-750.

## Olive in the prevention of various diseases

- [38] Schwartz B, Birk Y, Raz A, Madar Z. Nutritional-pharmacological combinations - a novel approach to reducing colon cancer incidence. *Eur J Nutr* 2004; 43: 221-229.
- [39] Liu J, Shimizu K, Kondo R. Anti-androgenic activity of fatty acids. *Chem Biodivers* 2009; 6: 503-512.
- [40] Hughes-Fulford M, Chen Y, Tjandrawinata RR. Fatty acid regulates gene expression and growth of human prostate cancer PC-3 cells. *Carcinogenesis* 2001; 22: 701-707.
- [41] Hamdi HK, Castellon R. Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor. *Biochem Biophys Res Commun* 2005; 334: 769-78.
- [42] Elamin MH, Daghestani MH, Omer SA, Elobeid MA, Virk P, Al-Olayan EM, Hassan ZK, Mohammed OB, Aboussekhra A. Olive oil oleuropein has anti-breast cancer properties with higher efficiency on ER-negative cells. *Food Chem Toxicol* 2013; 53: 310-316.
- [43] Hassan HK, Elamin MH, Omer SM, Daghestani MH, Al-Olayan ES, Elobeid MAR, Virk P. Oleuropein Induces Apoptosis Via the p53 Pathway in Breast Cancer Cells. *Asian Pac J Cancer Prev* 2013; 14: 6739-6742.
- [44] Cárdeno A, Sánchez-Hidalgo M, Rosillo MA, Alarcón de la Lastra C. Oleuropein, a secoiridoid derived from olive tree, inhibits the proliferation of human colorectal cancer cell through downregulation of HIF-1 $\alpha$ . *Nutr Cancer* 2013; 65: 147-56.
- [45] Huovinen R, Warri A, Collan Y. Mitotic activity, apoptosis and TRPM-2 mRNA expression in DMBA-induced rat mammary carcinoma treated with anti-estrogen toremifene. *Int J Cancer* 1993; 55: 685-691.
- [46] Hollowood K, Macartney JC. Reduced apoptotic cell death in follicular lymphoma. *J Pathol* 1991; 163: 337-342.
- [47] Jo EH, Hong HD, Ahn NC, Jung JW, Yang SR, Park JS, Kim SH, Lee YS, Kang KS. Modulations of the Bcl-2/Bax family were involved in the chemopreventive effects of licorice root (*Glycyrrhiza uralensis* Fisch) in MCF-7 human breast cancer cell. *J Agric Food Chem* 2004; 52: 1715-1719.
- [48] Mijatovic SA, Timotijevic GS, Miljkovic DM, Radovic JM, Maksimovic-Ivanic DD, Dekanski DP, Stosic-Grujicic SD. Multiple antimelanoma potential of dry olive leaf extract. *Int J Cancer* 2011; 128: 1955-1965.
- [49] Mateos R, Pereira-Caro G, Bacon JR, Bongaerts R, Sarriá B, Bravo L, Kroon PA. Anticancer Activity of Olive Oil Hydroxytyrosyl Acetate in Human Adenocarcinoma Caco-2 Cells. *J Agric Food Chem* 2013; 61: 3264-3269.
- [50] Li S, Han Z, Ma Y, Song R, Pei T, Zheng T, Wang J, Xu D, Fang X, Jiang H, Liu L. Hydroxytyrosol inhibits cholangiocarcinoma tumor growth: An in vivo and in vitro study. *Oncol Rep* 2014; 31: 145-152.
- [51] Huang YJ, Qi WX, He AN, Sun YJ, Shen Z, Yao Y. Prognostic Value of Tissue Vascular Endothelial Growth Factor Expression in Bladder Cancer: a Meta-analysis. *Asian Pac J Cancer Prev* 2013; 14: 645-9.
- [52] Adams J, Carder PJ, Downey S, Forbes MA, MacLennan K, Allgar V, Kaufman S, Hallam S, Bicknell R, Walker JJ, Cairnduff F, Selby PJ, Perren TJ, Lansdown M, Banks RE. Vascular endothelial growth factor (VEGF) in breast cancer: Comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen. *Cancer Res* 2000; 60: 2898-2905.
- [53] Shih CH, Ozawa S, Ando N, Ueda M, Kitajima M. Vascular endothelial growth factor expression predicts outcome and lymph node metastasis in squamous cell carcinoma of the esophagus. *Clin Cancer Res* 2000; 6: 1161-1168.
- [54] Mineta H, Miura K, Ogino T, Takebayashi S, Misawa K, Ueda Y, Suzuki I, Dictor M, Borg A, Wennerberg J. Prognostic value of vascular endothelial growth factor (VEGF) in head and neck squamous cell carcinomas. *Br J Cancer* 2000; 83: 775-781.
- [55] Heffelfinger SC, Miller MA, Yassin R, Gear R. Angiogenic growth factors in preinvasive breast disease. *Clin Cancer Res* 1999; 5: 2867-2876.
- [56] Santiago-Mora R, Casado-Diaz A, De Castro MD, Quesada-Gomez JM. Oleuropein enhances osteoblastogenesis and inhibits adipogenesis: the effect on differentiation in stem cells derived from bone marrow. *Osteoporos Int* 2011; 22: 675-84.
- [57] Sirianni R, Chimento A, De Luca A, Casaburi I, Rizza P, Onofrio A, Iacopetta D, Puoci F, Andò S, Maggiolini M, Pezzi V. Oleuropein and hydroxytyrosol inhibit MCF-7 breast cancer cell proliferation interfering with ERK1/2 activation. *Mol Nutr Food Res* 2010; 54: 833-40.
- [58] Thylefors B. The WHO program for the prevention of blindness. *Int J of ophthalmol* 1990; 14: 211.
- [59] Yokozawa T, Nakagawa T. *Food and Chemical Toxicology* 2004; 42: 975.
- [60] Jouad H, Haloui M, Rhiouani H, El Hilaly J, Edouks M. Ethnobotanical survey of medicinal plants used for the treatment of diabetes, cardiac and renal diseases in the North Center Region of Morocco (fez-Boulemane). *J Ethnopharmacol* 2001; 77: 175-182.
- [61] Gonzalez M, Zarzuelo A, Gamez MJ, Utrilla MP, Jimenez J, Osuna I. Hypoglycemic activity of olive leaf. *Planta Med* 1992; 58: 513-515.

## Olive in the prevention of various diseases

- [62] Somova LI, Shode FO, Ramnanan P, Nadar A. Antihyper-563 tensive, antiatherosclerotic and antioxidant activity of triterpenoids isolated from *Olea europaea*, subspecies *africana* leaves. *J Ethnopharmacol* 2003; 84: 299-305.
- [63] Huseini HF, Larijani B, Heshmat R, Fakhrzadeh H, Radjabipour B, Toliat T, Raza M. The efficacy of *Silybum marianum* (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. *Phytother Res* 2006; 20: 1036-1039.
- [64] Said O, Fulder S, Khalil K, Azaizeh H, Kassis E, Saad B. Maintaining a physiological blood glucose level with "Glucoselevel", a combination of four anti-diabetes plants used in the traditional arab herbal medicine. *Evid Based Complement Alternat Med* 2008; 5: 421-428.
- [65] Chandler D, Woldu A, Rahmadi A, Shanmugam K, Steiner N, Wright E, Benavente-García O, Schulz O, Castillo J, Munch G. Effects of plant-derived polyphenols on TNF-alpha and nitric oxide production induced by advanced glycation endproducts. *Mol Nutr Food Res* 2010; 54: S141-S150.
- [66] Komaki E, Yamaguchi S, Maru I, Kinoshita M, Kakehi K, Ohta Y, Tsukada Y. Identification of anti-alpha-amylase components from olive leaf extracts. *Food Sci Technol Res* 2003; 9: 35-39.
- [67] Al-Azzawie HF, Alhamdani MS. Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. *Life Sci* 2006; 78: 1371-7.
- [68] Jemai H, El Feki A, Sayadi S. Antidiabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats. *J Agric Food Chem* 2009; 57: 8798-804.
- [69] Eidi A, Eidi M, Darzi R. Antidiabetic effect of *Olea europaea* L. In normal and diabetic rats. *Phytother Res* 2009; 23: 347-50.
- [70] Mangerich A, Bürkle A. Pleiotropic cellular functions of PARP1 in longevity and aging: genome maintenance meets inflammation. *Oxid Med Cell Longev* 2012; 2012: 321653.
- [71] Trichopoulou A, Critselis E. Mediterranean diet and longevity. *Eur J Cancer Prev* 2004; 13: 453-456.
- [72] Cañuelo A, Gilbert-López B, Pacheco-Liñán P, Martínez-Lara E, Siles E, Miranda-Vizuete A. Tyrosol, a main phenol present in extra virgin olive oil, increases lifespan and stress resistance in *Caenorhabditis elegans*. *Mech Ageing Dev* 2012; 133: 563-574.
- [73] Katsiki M, Chondrogianni N, Chinou I, Rivett AJ, Gonos ES. The olive constituent oleuropein exhibits proteasome stimulatory properties in vitro and confers life span extension of human embryonic fibroblasts. *Rejuvenation Res* 2007; 10: 157-172.
- [74] Roe DA. Current etiologies and cutaneous signs of vitamin deficiencies. In: Roe DA, ed. *Nutrition and the skin. Contemporary issues in clinical nutrition*. New York: Alan R Liss Inc 1986; pp: 81-98.
- [75] Viola P, Nobili F, Viola M. Handbook of diet, nutrition and the skin. *Human Health Handbooks no. 1. Olive oil as a skin protector* 2012; 2: 282-299.
- [76] Ancora C, Roma C, Vettor M. Evaluation of cosmetic efficacy of oleuropein. *Symposium on the New Frontiers of Dermo-cosmetology: Efficacy, Stability and Safety*. Rome, Italy, November 4-6; 2004.
- [77] Kimura Y, Sumiyoshi M. Olive leaf extract and its main component oleuropein prevent chronic ultraviolet B radiation-induced skin damage and carcinogenesis in hairless mice. *J Nutr* 2009; 139: 2079-2086.
- [78] Gonzalez-Correa JA, Munoz-Marin J, Arrebola MM, Guerrero A, Narbona F, Lopez-Villodres JA, De La Cruz JP. Dietary virgin olive oil reduces oxidative stress and cellular damage in rat brain slices subjected to hypoxia-reoxygenation. *Lipids* 2007; 42: 921-9.
- [79] Gonzalez-Correa JA, Navas MD, Lopez-Villodres JA, Trujillo M, Espartero JL, De La Cruz JP. Neuro-protective effect of hydroxytyrosol and hydroxytyrosol acetate in rat brain slices subjected to hypoxia-reoxygenation. *Neurosci Lett* 2008; 446: 143-6.
- [80] Bu Y, Rho S, Kim J, Kim MY, Lee DH, Kim SY, Choi H, Kim H. Neuro-protective effect of tyrosol on transient focal cerebral ischemia in rats. *Neurosci Lett* 2007; 414: 218-21.
- [81] Mohagheghi F, Bigdeli MR, Rasouljan B, Zein-anloo AA, Khoshbaten A. Dietary virgin olive oil reduces blood brain barrier permeability, brain edema, and brain injury in rats subjected to ischemia-reperfusion. *ScientificWorldJournal* 2010; 10: 1180-91.
- [82] De La Cruz JP, Del Rio S, Arrebola MM, Lopez-Villodres JA, Jebrouni N, Gonzalez-Correa JA. Effect of virgin olive oil plus acetylsalicylic acid on brain slices damage after hypoxia-reoxygenation in rats with type 1-like diabetes mellitus. *Neurosci Lett* 2010; 471: 89-93.
- [83] Pitozzi V, Jacomelli M, Zaid M, Luceri C, Bigagli E, Lodovici M, Ghelardini C, Vivoli E, Norcini M, Gianfriddo M, Esposito S, Servili M, Morozzi G, Baldi E, Bucherelli C, Dolara P, Giovannelli L. Effects of dietary extra-virgin olive oil on behaviour and brain biochemical parameters in ageing rats. *Br J Nutr* 2010; 103: 1674-83.
- [84] Khalatbary AR, Ahmad H. Effect of Oleuropein on Tissue Myeloperoxidase Activity in Experimental Spinal Cord Trauma. *Iran Biomed J* 2011; 15: 164-167.

## Olive in the prevention of various diseases

- [85] Bazoti FN, Bergquist J, Markides K, Tzarbopoulos A. Noncovalent Interaction between Amyloid- $\beta$ -Peptide (1-40) and Oleuropein Studied by Electrospray Ionization Mass Spectrometry. *J Am Soc Mass Spectrom* 2006; 17: 568-575.
- [86] Rabiei Z, Bigdeli MR, Rasouljan B, Ghassempour A, Mirzajani F. The neuroprotection effect of pretreatment with olive leaf extract on brain lipidemics in rat stroke. *Phytomedicine* 2012; 19: 940-6.