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

Olive 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, remediing 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 B4 [27]. Another supportive evidence of Olive leaf extract functions as anti-inflammatory properties and inhibition of platelet aggregation and thromboxane A2 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
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 μM oleuropein as compared to untreated cells and cells treated with 200 μM 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-1α 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 hormetic mechanisms. Other constituents (oleuropein-treated cultures) exhibit a delay or slowdown 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.
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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 Aβ 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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