Chapter 2
Beneficial Effects of Extra Virgin Olive Oil (n-9 Fatty Acids) on Neurological Disorders

2.1 Introduction

Olive oil is used by humans for food since prehistoric times. Olive oil not only contains oleic acid (18:1n-9), but also small amounts of other fatty acids, such as palmitic, palmitoleic, stearic, linoleic, and α-linolenic acids and squalene (Fig. 2.1). In addition to fatty acids, olive oil also contains phenolic compounds. Oleic acid, a monounsaturated nonessential fatty acid, belongs to n-9 family of fatty acids. It is found in animals and plants and represents a large proportion of human dietary intake with low uptake by liver and brain. Beef and poultry contain 30–45 % oleic acid, while oils such as palm, peanut, soybean, grape seed oil, and sunflower contain 25–49 % oleic acid (Waterman and Lockwood 2007). Other sources of oleic acid include avocado fruit (50 %), Macadamia nuts (45 %), apricot seeds (35 %), almonds (33 %), and olive oil (55–80 %). Among various cooking oils, olive oil is unique because it has high oleic acid content. In contrast, majority of other cooking oils (palm, peanut, soybean, and sunflower) are composed primarily of n-6 polyunsaturated fatty acids. The presence of one double bond makes oleic acid not only less susceptible to oxidation, but also contributes to the high stability and long shelf life of olive oil (Owen et al. 2000a, b).

Dietary fat intake modulates fatty acid composition of membranes, which in turn regulates activities of many membrane proteins, receptors, and ion channels in various body tissues. Thus, Mediterranean diet, which is rich in olive oil, increases the levels of oleic acid in plasma membrane phospholipids from various tissues in rat and human cells (Escudero et al. 1998; Vicario et al 1998). Conversion of stearic acid into oleic acid is catalyzed by stearoyl-CoA desaturase (SCD). This enzyme in association with NADPH, cytochrome b5 reductase, and cytochrome b5 and in the presence of molecular oxygen inserts a single double bond (between carbons 9 and 10) into stearoyl-CoAs (Ntambi and Miyazaki 2004). Oleic acid then becomes a major substrate for the synthesis of various lipids including phospholipids, triglycerides, and cholesteryl esters. Other fatty acids (linoleic acid, α-linolenic acid, arachidonic acid, and docosahexaenoic acid, which are also components of the membrane

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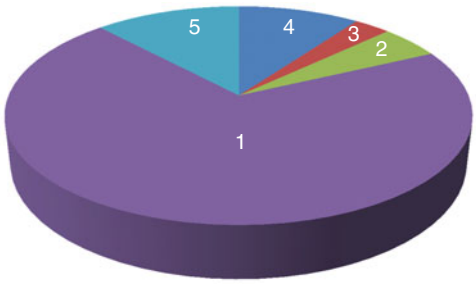

Fig. 2.1 Proprotions of various fatty acids found in extra virgin olive oil. Oleic acid (1); stearic acid (2); palmitoleic acid (3); linoleic acid (4); and palmitic acid (5)

phospholipids) are not synthesized by human cells and must be taken in through the diet. Studies on fatty acid composition in human brain indicate that in the younger humans, the polyunsaturated fatty acids are generally decreased with age, with the exception of docosahexaenoic acid that shows a significant increase. In humans, levels of monounsaturated fatty acids, such as oleic acid are increased to the age of 18 years. Several other polyunsaturated fatty acids particularly arachidonic acids are also decreased with age in the older subjects. The levels of linoleic acid, however, are increased significantly with age in the older humans. In the older human subjects, there is a significant relationship between brain and erythrocyte levels for several fatty acids, particularly hexadecanoic acid, suggesting that levels of cerebral cortex fatty acids change from early childhood through late adulthood; late adulthood erythrocyte fatty acid levels may be useful in predicting brain fatty acid levels in adults (Carver et al. 2001). Alterations in fatty acid composition of membrane are known to influence the localization and activity of G proteins and protein kinase C (PKC) (Escribá et al. 1997). PKC and G proteins play an important role in signaling and in regulating blood pressure (Escribá et al. 2003). Although the molecular mechanism associated with above processes is not fully understood, but elevation in oleic acid levels increases hexagonal phase propensity and induces fluidification effect in the lamellar phase resulting into densely packed membrane, which is more receptive to signals that reduce blood pressure. In contrast, elaidic acid and stearic acid produce no such effect on membrane propensity and fluidification (Prades et al. 2003; Funari et al. 2003). Collective evidence suggests that membrane fatty acid composition not only modulates physical properties, such as structure, fluidity/viscosity, permeability, microdomain formation, and shear stress, but also gene expression and activities of enzymes (adenylyl cyclase and phospholipase C), receptors, ion channels, and generation of second messengers (Khan et al. 1992; Ntambi and Bené 2001).

2.2 Chemical Composition and Biochemical Activities of Components of Olive Oil

As stated earlier, oleic acid is a major component of olive oil, which unlike most dietary oils that are manufactured from the seeds of plants by means of solvent extraction and refined before being edible, olive oil is obtained from the whole fruit

of *Olea europaea* L. only by physical pressure. This method makes extra virgin olive oil unique because several chemical components that cannot be found in other dietary oils are transferred from the leaves and skin of olives to the olive oil. The hydrocarbon composition of extra virgin olive oil is different from other edible oils. Thus in the unsaponifiable fraction, extra virgin olive oil contains high levels of squalene, a polyunsaturated triterpene, which is a precursor for the biosynthesis of cholesterol and steroid hormones (Perona et al. 2006). The main sterol component of extra virgin olive is β-sitosterol, which makes 95 % of sterol fraction. In addition, minor quantities of campesterol, D7-stigmastenol, stigmasterol, spinasterol, and avenasterol are also found in olive oil. Olive oil also contains α, β, γ-tocopherols, which account for more than 85 % of the total tocopherols (Perona et al. 2006).

It is well known that neurons utilize glucose as the primary energy source (Sokoloff et al. 1977). However, some hypothalamic neurons also utilize long-chain fatty acids as signaling molecules (Migrenne et al. 2006; Jo et al. 2009). In vivo, the ability of hypothalamic neurons to sense fatty acids affects insulin secretion, hepatic glucose production, and food intake (Migrenne et al. 2006). Thus, studies on the utilization of oleic acid by VMN neurons indicate that dissociated ventromedial hypothalamic nucleus (VMN) neurons utilize oleic acid and physiological concentrations of hypothalamic glucose (Silver and Erecinska 1994; De Vries et al. 2003) as a potential means of sensing and regulating energy homeostasis in the body. Although the molecular mechanism associated with this process is not fully understood, interactions between oleic acid and fatty acid transporter CD36, a member of class B scavenger receptor proteins, may play an important role (Le Foll et al. 2009). It is proposed that CD36 interactions with oleic acid alters neuronal activity in a manner analogous to that utilized for fat perception by taste receptor cells (Laugerette et al. 2005). The binding of oleic acid with CD36 induces the phosphorylation of protein tyrosine kinases, leading to generation of inositol 1,4,5-trisphosphate, recruitment of calcium from the endoplasmic reticulum, followed by influx of calcium via opening of store-operated calcium channels, membrane depolarization, and neurotransmitter release (El-Yassimi et al. 2008. Based on detailed investigation, it is suggested that VMN metabolic sensing neurons respond to glucose and fatty acid through two distinct and largely unrelated mechanisms (Le Foll et al. 2009). One involving fatty acid sensing through binding to cell surface receptors with activation of downstream signaling cascades, and the other requires glucose sensing primarily by intracellular glucose metabolism and influx of calcium through voltage-dependent calcium channels (Le Foll et al. 2009).

Oleic acid directly regulates the electrical activity of pro-opiomelanocortin (POMC) neurons in hypothalamus, enhancing the anorexigenic tone exerted by the melanocortinergic system. These neurons not only respond to circulating signals—such as glucose, leptin, insulin, ghrelin, and peptide YY (Jo et al. 2009), but also contribute to the regulation of energy expenditure by releasing the anorexigenic melanocyte-stimulating hormones (α-MSH and γ-MSH) through the activation of centrally expressed melanocortin-3 (MC3R) and melanocortin-4 receptors (MC4Rs) (Mountjoy and Wong 1997). The mitochondrial β-oxidation of oleic acid is a critical step in the regulation of the excitability of POMC neurons. The regulation of K_{ATP} channels in POMC neurons by both acute and long-term treatment with oleic

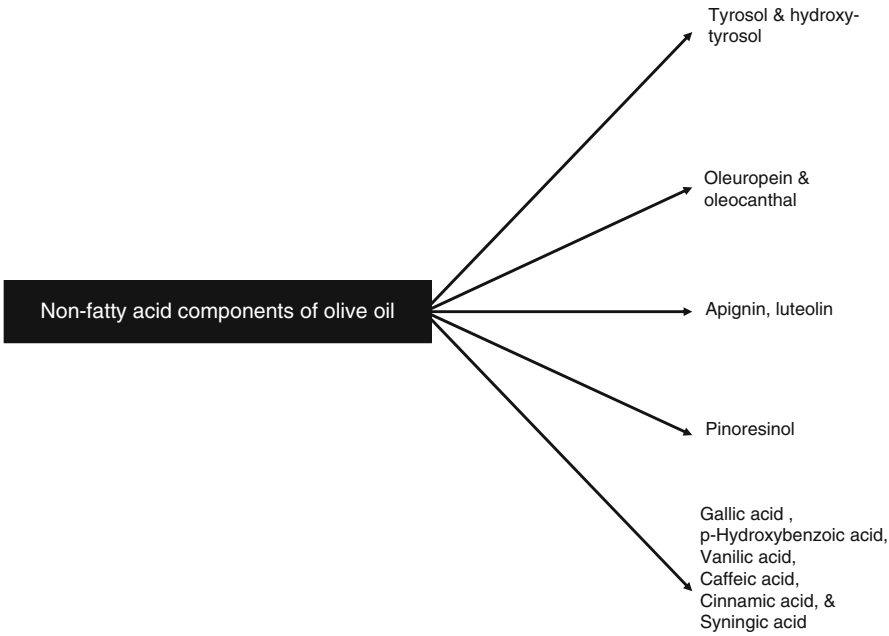

Fig. 2.2 Nonfatty acid components of olive oil

acid and nutrient-related hormones may contribute to the control of food intake and to the maintenance of weight balance (Jo et al. 2009).

The phenolic compounds of olive oil can be divided into three categories: simple phenols, secoiridoids, and lignans. All these components inhibit autooxidation. Major nonfatty acid components of olive oil include hydroxytyrosol, tyrosol, oleuropein, apignin, luteolin, pinoresinol, caffeic acid, vanillic acid, syringic acid, p-coumaric acid, o-coumaric acid, protocatechuic acid, 4-hydroxybenzoic acid, 4-hydroxyphenylacetic acid, and 3,4-dihydroxyphenylacetic acid (Owen et al. 2000a, b; Alarcón de la Lastra et al. 2001; Perona et al. 2006) (Fig. 2.2). The olives mainly contain the polar glycosides oleuropein and ligstroside. Oleuropein is the ester of elenolic acid with 3,4′- dihydroxyphenylethanol (hydroxytyrosol), and ligstroside is the ester of elenolic acid with 4-hydroxyphenylethanol (tyrosol). Oleuropein and ligstroside are the parent compounds of the less polar oleuropein- and ligstroside-aglycones. Oleuropein- and ligstroside-aglycones are produced by the removal of the glucose moiety from the oleuropein- and ligstroside-glycoside by β-glucosidase during olive ripening process (Fig. 2.3) (Martinez-Dominguez et al. 2001; Granados-Principal et al. 2010). Those aglycones and their various derivatives are the most abundant phenols in olive oil. Thus, hydroxytyrosol and tyrosol are simple phenols and oleuropein is a secoiridoid (Fig. 2.4).

In cardiovascular system, studies on the effect of monoacylglycerols containing palmitic acid (MAG-P), stearic acid (MAG-S), or oleic acid (MAG-O) at the sn-2 position of glycerol moiety indicate that not only MAG-O shows the strongest

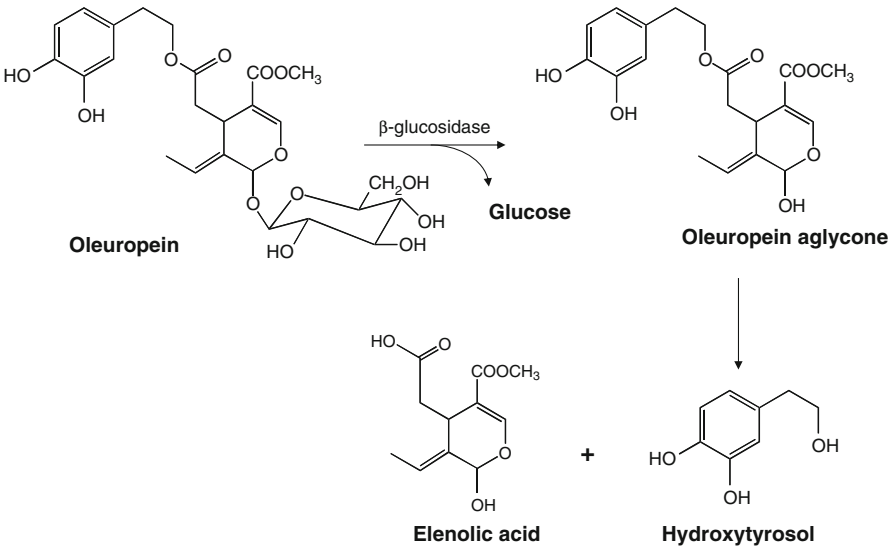

Fig. 2.3 Scheme showing the generation of hydroxytyrosol from oleuropein

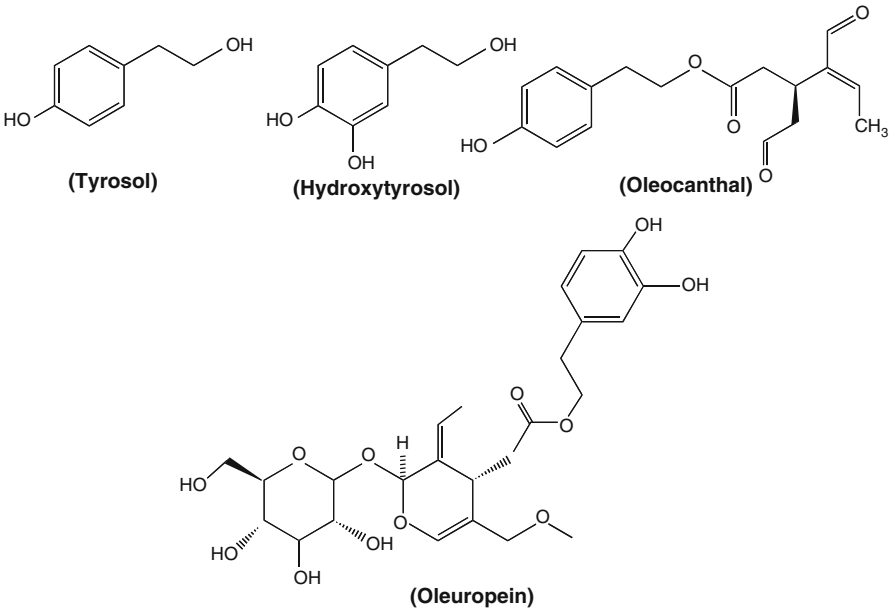

Fig. 2.4 Chemical structures of polyphenols found in extra virgin olive oil

inhibition of LDL-PLA_2 and antiatherogenic activities, but also MAG-S and MAG-P show adequate inhibitory activity (Cho et al. 2010). In contrast, MAG-S and MAG-P show stronger paraoxonase (PON)-enhancing activity than MAG-O. In recent years, PON has emerged as the component of HDL most likely to explain its ability to attenuate the oxidation of LDL. Thus, PON might be a major defense barrier against lipid peroxides from oxLDL. High intake of oleic acid is associated with significantly increased HDL-cholesterol concentrations and PON activity (Tomas et al. 2001). It is also reported that HDL rich in oleic acid was less prone to be oxidized, indicating that dietary oleic acid in MUFA prevents the oxidative modification of HDL (Sola et al. 1997). Although the exact mechanism of MAG-O-mediated atherogenic effect is not fully understood, it is proposed that inhibition of LDL-PLA_2 may be closely associated with atherogenic effect. In addition, MAG-O also shows the strongest antioxidant activity against copper-mediated LDL oxidation, indicating that oleic acid-containing MAG enhances the antioxidant ability against copper-mediated LDL oxidation. Oleic acid has been reported to exert beneficial effects on the pathogenesis of vascular disease via protection of LDL from oxidation (Mata et al. 1997) and to induce less monocyte chemotaxis and adhesion on exposure to oxidative stress (Tsimikas et al. 1999; Reaven et al. 1991). Collective evidence suggests that above activities may contribute to increased antiatherogenic potential of MAG-O and are associated with beneficial effects of oleic acid on human health.

2.2.1 Bioavailability and Metabolism of Olive Oil Components

Many studies have shown that the phenolic compounds (hydroxytyrosol, tyrosol, oleuropein, and oleuropein-aglycone) are absorbed after ingestion in a dose-dependent manner (Vissers et al. 2002; Edgecombe et al. 2000; Tuck et al. 2001). The mechanism underlying absorption of olive oil phenolic compounds remains unclear. However, different polarities of various phenolics have been postulated to play an important role in the absorption of these compounds (Vissers et al. 2002). For example, tyrosol and hydroxytyrosol are polar compounds and their absorption takes place through the passive diffusion (Manna et al. 2000). The polar but larger phenolic, oleuropein-glycosides are absorbed via a glucose transporter-mediated process involving carrier Na-dependent glucose transporter 1. In addition, oleuropein-glycoside can also be absorbed via the paracellular route or transcellular passive diffusion (Edgecombe et al. 2000). Among phenolic compounds of olive oil, oleuropein-glycoside and oleuropein and ligstroside-aglycones are metabolized to hydroxytyrosol or tyrosol and excreted in urine (Vissers et al. 2002). In addition, hydroxytyrosol and tyrosol can also be conjugated to glucuronic acid and excreted in urine as glucuronides (Vissers et al. 2002; Visioli et al. 2001). Hydroxytyrosol may also be O-methylated in vivo as judged by the presence of homovanillic acid (a well-known metabolite of dopamine) and homovanillyl alcohol in human and animal plasma and urine after olive oil ingestion (Visioli et al. 2003). Even in

moderate dose (25 ml/day), which is lower than the traditional daily dietary intake in Mediterranean countries, around 98 % of these phenolics are present in plasma and urine in conjugated forms, mainly as glucuronides. This suggests the existence of an extensive first-pass intestinal/hepatic metabolism of the ingested tyrosol and hydroxytyrosols in the extra virgin olive oil. Tyrosol also binds to low density lipoproteins (LDL). This binding is directly related to an increase of the LDL resistance to oxidation (Covas et al. 2000). Ingestion of olive oil rich in phenolic compounds for 1 week leads to an increase in the total phenolic content of LDL in human subjects (Covas et al. 2000). Collective evidence suggests that once absorbed, olive oil phenolic compounds undergo extensive metabolism in liver and kidney, where they may play an important role in the prevention of oxidative stress and inflammation.

Hydroxytyrosol is known to enter brain tissue (Wu et al. 2009). Studies on hydroxytyrosol-fed mice brain slices indicate that hydroxytyrosol exerts a dose-dependent decrease in the efflux of lactate dehydrogenase demonstrating the neuroprotective potentials of hydroxytyrosol in rodent model of hypoxia (González-Correa et al. 2008). Treatment of PC12 cells with olive mill waste water extract, which is enriched in hydroxytyrosol indicates that this component of olive oil has cytoprotective effect on PC12 cells (Schaffer et al. 2007, 2010). Hydroxytyrosol acts by inducing the nuclear transcription factor erythroid 2p45-related factor (Nrf2), a transcription factor implicated in the expression of several antioxidant/detoxificant enzymes. Thus, hydroxytyrosol activates two important signaling proteins involved in Nrf2 translocation, the protein kinase B and the extracellular regulated kinases. Studies on the effect of specific inhibitors support the involvement of both molecular pathways for the nuclear translocation of Nrf2. Accumulating evidence suggests that in addition to inherent radical scavenging activity, hydroxytyrosol acts through an additional mechanism, namely, Nrf2 pathway to prevent oxidative stress damage (Martin et al. 2010). It should also be noted that hydroxytyrosol exists in the brain as an endogenous neurotransmitter, such as dopamine and norepinephrine, which are formed via monoamino oxidase-catalyzed deamination and subsequent reduction. Therefore, it is likely that hydroxytyrosol exerts endogenous antioxidant activity in the brain tissue by interacting selectively within signaling cascades, such as tyrosine kinase, PtdIns 3-kinase/Akt, PKC and MAP kinase pathways. These pathways regulate cell survival following exposure to oxidative stress (Visioli et al. 2000).

Health benefits of Mediterranean diet are not only related to the presence of oleic acid and phenolic compounds, but also other components, such as cereals, grains, fish, nuts, fruits, vegetables, and red wine, which are rich in phenols, flavonoids, isoflavonoids, phytosterols, and phytic acid—essential bioactive compounds providing health benefits. Oleic acid is converted into nitrated oleic acid (nitro-oleic acid) in the presence of nitric oxide ($NO^{\bullet}$). Nitrated oleic is found in the plasma and several tissues including brain, where it not only inhibits neuroinflammation, but also promotes blood vessel relaxation through modulation of macrophage activation and prevention of leukocyte and platelet activation (Trostchansky and Rubbo 2008). Phenolic components of olive oil contribute to lower rates of cardiovascular disease,

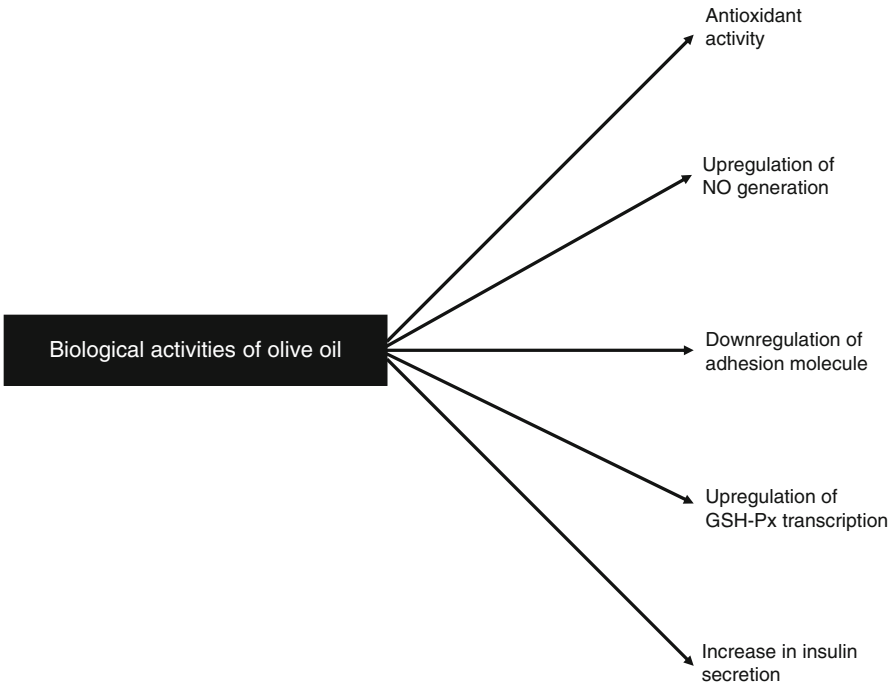

Fig. 2.5 Biological activities of extra virgin olive oil

cancer, and age cognitive decline (Perez-Jimenez et al. 2005; Lopez-Miranda et al. 2007). Olive oil also decreases blood pressure and protects from diabetes. Olive oil not only provides the higher percent of energy but the presence of bioactive polyphenolic compounds promotes human health not only by their antioxidant activities, but also through upregulation of nitric oxide synthase and gluthathione peroxidase and increase in insulin secretion (Fig. 2.5). As mentioned earlier, the presence of one double bond and polyphenolic antioxidants increases the shelf life of olive oil compared to other vegetable oils. These phenols have many beneficial effects on human neurovascular and cardiovascular systems.

2.2.2 Biochemical Effects of Olive Oil Phenolic Compound on Heart

As stated before, olive oil contains tyrosol [2-(4-hydroxyphenyl)ethanol], hydroxytyrosol, oleuropein, and oleocanthal (Fig. 2.3), and has a balanced ratio of monounsaturated and polyunsaturated fatty acids (Ruano et al. 2005; Covas et al. 2006; Carluccio et al. 2007). Supplementation of olive oil in human diet improves the

Table 2.1 Fatty acid and nonfatty acid components of extra virgin olive oil

Saponificable components and reference	Nonsaponificable components and reference	Nonfatty components and reference
Oleic acid (Granados-Principal et al. 2010)	Nonglycerides (Granados-Principal et al. 2010)	Tyrosol (Bendini et al. 2007)
Palmitic acid (Granados-Principal et al. 2010)	Aliphatic alcohol (Granados-Principal et al. 2010)	Hydroxytyrosol (Bendini et al. 2007)
Linoleic acid (Granados-Principal et al. 2010)	Triterpene alcohol (Granados-Principal et al. 2010)	Oleuropein (Bendini et al. 2007)
Stearic acid (Granados-Principal et al. 2010)	Sterols (Granados-Principal et al. 2010)	Oleocanthal (Bendini et al. 2007)
Palmitoleic acid (Granados-Principal et al. 2010)	Carotenoids (Granados-Principal et al. 2010)	Apignin (Bendini et al. 2007
Linolenic acid (Granados-Principal et al. 2010)	Squalene (Granados-Principal et al. 2010)	Luteolin (Bendini et al. 2007)
Myristic acid (Granados-Principal et al. 2010)	Pigments (Granados-Principal et al. 2010)	Pinoresinol (Bendini et al. 2007)
–	–	Gallic acid (Bendini et al. 2007)

major risk factors for cardiovascular disease, such as the lipoprotein profile, blood pressure, glucose metabolism, and antithrombotic profile (Perez-Jimenez et al. 2005). In addition, olive oil contains many other components, such as phenolic acids, lignans, and flavonoids (Table 2.1), which may promote many beneficial effects on human health. Multiple mechanisms have been proposed to explain beneficial effects of Mediterranean diet. These mechanisms include: decrease in LDL-cholesterol, increase HDL-cholesterol, and reduction of oxidative stress due to polyphenols and flavonoids, which may act as scavengers and protect heart tissue and LDL from free radical damage. Components of Mediterranean diet diminish NF-κB activation in mononuclear cells compared to Western diet (Pérez-Jiménez et al. 2007). Thus, extra virgin olive oil extracts inhibit the translocation of NF-κB subunits in both unstimulated and phorbol-myristate acetate (PMA)-stimulated monocytes and monocyte-derived macrophages (Brunelleschi et al. 2007) (Fig. 2.6). This effect occurs at concentrations of tyrosol and hydroxytyrosol found in human plasma after nutritional ingestion of extra virgin olive oil and is quantitatively similar to the effect exerted by ciglitazone, a PPAR-γ ligand. However, extra virgin olive oil extract has no effect on PPAR-γ expression in monocytes. These results support the view that the beneficial effects of extra virgin olive oil are due to its ability to inhibit NF-κB activation in human monocyte/macrophages (Brunelleschi et al. 2007). In RAW 264.7 macrophages, tyrosol not only inhibits exogenous ROS-mediated [^{3}H]arachidonic acid (ARA) release, but also alters PMA-mediated nitric oxide generation (Moreno 2003). Oleuropein, an antioxidative and anti-ischemic compound found in extra virgin olive oil inhibits the adhesion of monocyte cells to the blood vessel lining, a process closely associated with the development of atherosclerosis. Another beneficial component of olive oil is oleuropein, a member of the secoiridoid family, which is hydrolyzed into the hydroxytyrosol and functions as a

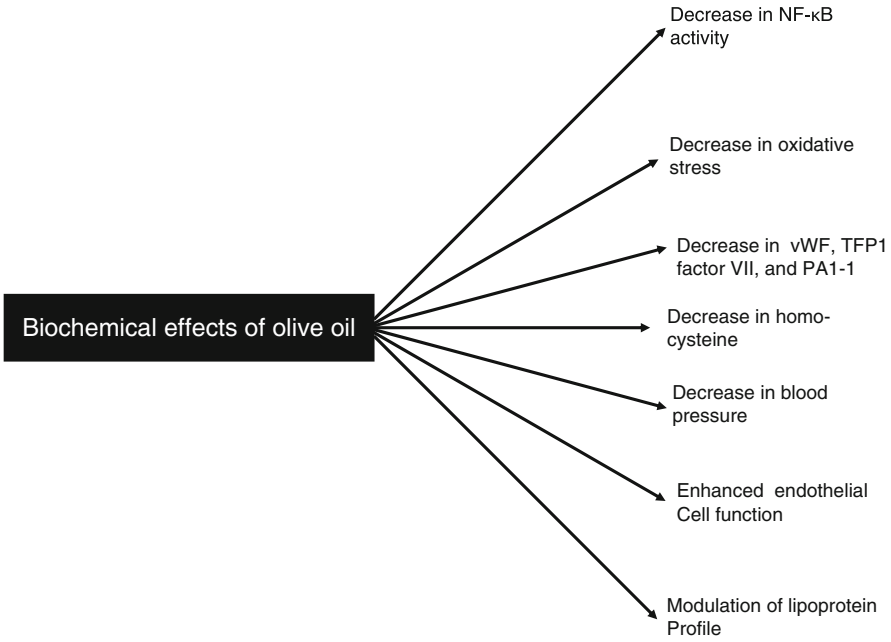

Fig. 2.6 Neurochemical activities of extra virgin olive oil

hydrophilic phenolic antioxidant that is oxidized to its catechol quinone during redox cycling (Cornwell and Ma 2008). Little is known about the biological properties of the catechol hydroxytyrosol quinone, a strong arylating electrophile that forms Michael adducts with thiol nucleophiles in glutathione and proteins. These properties may contribute to the unique nutritional benefits of olive oil. Oleocanthal is another olive oil component that inhibits cyclooxygenases, enzymes responsible for the oxidation of ARA into prostaglandins and thromboxanes. This property is similar to ibuprofen, a nonsteroidal drug with anti-inflammatory, analgesic, and antipyretic properties (Beauchamp et al. 2005; Smith et al. 2007). Diet enriched in virgin olive oil reduces the sensitivity of platelets to aggregate by decreasing von Willebrand and thromboxane B_2 plasma levels (Perez-Jemenez et al. 2006; Ruano et al. 2007). Olive oil components not only decrease activities of vWF, TFP1, and PA1-1 factors, but also decrease homocysteine levels, enhance endothelial cell function, and modulate lipoprotein profiles (Fig. 2.6). The ability of extra virgin olive oil to decrease fasting factor VII (proconvertin) in plasma results in the modulation of postprandial activation, a process which is important in relation to its heart protective effect (Lopez-Miranda et al. 2007). In addition, extra virgin olive oil also prevents inflammation by inhibiting platelet activating factor, a lipid mediator that plays an important role not only in clotting process, but also by activating immune cells and their binding to the endothelial wall (Karantonis et al. 2006). Hydroxytyrosol and oleuropein are potent scavengers. They scavenge superoxide anion and other reactive

species (peroxynitrite, hypochlorous acid) possibly implicated in the onset of heart disease. Moreover, hydroxytyrosol and oleuropein are also capable to modulate enzymic processes (Visioli et al. 2002). For example, hydroxytyrosol has been shown to inhibit platelet aggregation, suggesting it has antithrombotic potentials (Correa et al. 2009). Accumulating evidence indicates that olive oil components interfere with the inflammatory response within atherosclerotic lesion by blocking endothelial activation and inhibiting inflammatory cytokines production and secretion in macrophages, and modulating matrix-degrading enzymes. Accumulating evidence suggests that olive oil in Mediterranean diet not only improves the endothelium-dependent vasodilatory response and stabilizes local vascular tone, but also produces antithrombotic and anti-inflammatory effects through the oleocanthal-mediated inhibition of COX-1 and COX-2 (Bogani et al. 2007; Beauchamp et al. 2005). In addition, olive oil intake also modulates immune fuction. These processes improve vascular stability (Carluccio et al 2007; Ruano et al. 2005; Fuentez et al. 2008).

$NO^{\bullet}$ is a free radical signaling mediator generated by the healthy endothelium to maintain vascular homeostasis through the regulation of blood pressure and leukocyte–platelet activation. Elevation of $NO^{\bullet}$ levels is accompanied by its rapid transformation into potent nitrating and nitrosating species, including peroxynitrite ($ONOO^{-}$), nitrogen dioxide (NO_2), and nitrous acid (HONO). These species can react with unsaturated lipids, forming both oxidized and nitrated products, including nitro, nitrito, and nitroepoxy derivatives (Rubbo et al. 1994). The reaction of oleic acid with $NO^{\bullet}$- and nitrite (NO_2^{-})-derived species yields nitrated oleic acid (Villacorta et al. 2007). Although the mechanisms of biological fatty acid nitration remain incompletely characterized, recent studies reveal that during oleic acid nitration, vinyl nitro regioisomers represent a component that displays distinctive chemical reactivity and receptor-dependent signaling actions (Villacorta et al. 2007). Similarly, the molecular mechanisms associated with biochemical actions of nitrated oleic acid remain unknown. However, it is becoming increasingly evident that nitrated derivatives of oleic and linoleic acid inhibit leukocyte and platelet activation (Coles et al. 2002), vascular smooth muscle proliferation (Villacorta et al. 2007), lipopolysaccharide-stimulated macrophage cytokine secretion (Cui et al. 2006) (17), activate peroxisome proliferator-activated receptor-γ (Schopfer et al. 2005a), and induce endothelial heme oxygenase 1 expression (Wright et al. 2006) (Fig. 2.7). NO_2-fatty acid also potently modulates nuclear factor-erythroid 2-related factor 2/Kelch-like ECH-associating protein 1 (Nrf2/Keap1) (Villacorta et al. 2007; Cui et al. 2006) and nuclear factor κB (NFκB)-regulated inflammatory signaling (Cui et al. 2006). Nrf2 governs the expression of ARE-regulated genes (Nguyen et al. 2003). Under physiological conditions, Nrf2 is normally retained in the cytoplasm by the repressor protein Keap1 (Nguyen et al. 2003). Keap1 contains highly reactive sulfhydryl groups and acts as a cellular sensor that recognizes electrophilic inducers (Wakabayashi et al. 2004). In response to oxidative stress or glutathione depletion or nitrosative stress, such as generation of nitrated oleic acid, Nrf2/Keap1 complex dissociates, and Nrf2 translocates to the nucleus where it interacts with ARE and coordinates transcription of a collection of cytoprotective and detoxification genes, such as heme oxygenase-1 (Prestera et al. 1995), glutathione-*S*-transferases (GSTs),

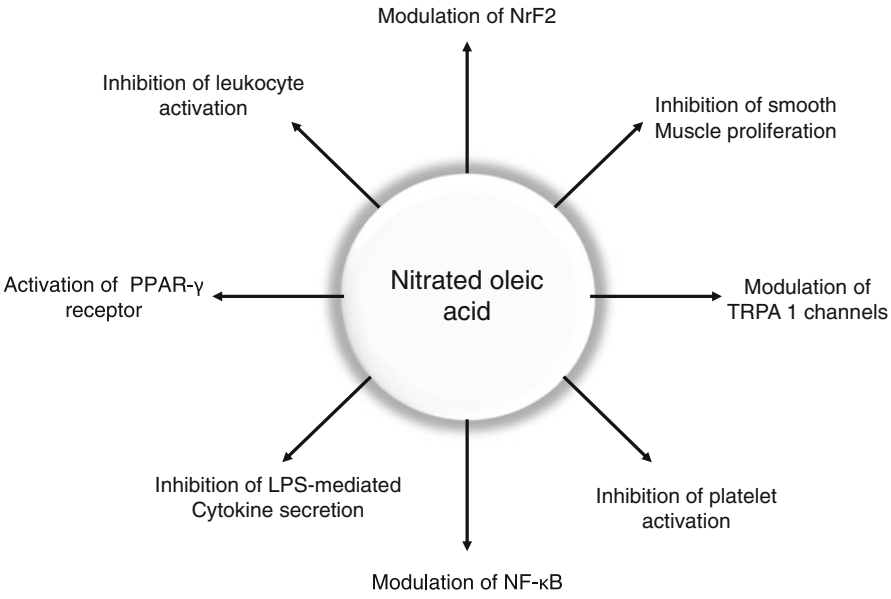

Fig. 2.7 Biolchemical activities of nitrated oleic acid

NADH quinine oxidoreductase, γ-glutamylcystein ligase (γ-GCL) (Prestera and Talalay 1995), and NAD(P)H:quinone oxidoreductase 1 (Li and Jaiswal 1992). These enzymes provide efficient cytoprotection, in part, by regulating the intracellular redox state. Their induction contributes to protection from a variety of toxins in a variety of cells including neuronal and astrocytic cultures (Shih et al. 2003). It is also reported that micellar and membrane stabilization of nitrated fatty acid prevents NeF-like aqueous decay reactions and consequent $NO^{\bullet}$ release, supporting that the predominant signaling actions mediated by nitrated fatty acids are $NO^{\bullet}$ and cGMP independent (Schopfer et al. 2005b; Lima et al. 2005) (Fig. 2.8). In addition, xanthine oxidoreductase (XOR), a molybdoflavin protein that serves as the rate-limiting enzyme in the terminal steps of purine degradation in humans, catalyzing the oxidation of hypoxanthine to xanthine and finally to uric acid is irreversibly inhibited by nitrated oleic acid. During inflammatory process, reversible oxidation of critical cysteine residues or limited proteolysis converts XDH to xanthine oxidase (XO), which reduces O_2 to superoxide and hydrogen peroxide (H_2O_2) (Harrison 2002). Conversion to XO is not required for reactive oxygen species (ROS) generation because xanthine dehydrogenase displays partial oxidase activity (Harris and Massey 1997). The generation of ROS in the vascular compartment enhances redox-dependent signaling supporting a key role of XOR in oxidative stress and inflammatory processes. It should be noted that despite the significant advances on health benefits of olive oil in heart disease, the molecular mechanism(s) associated

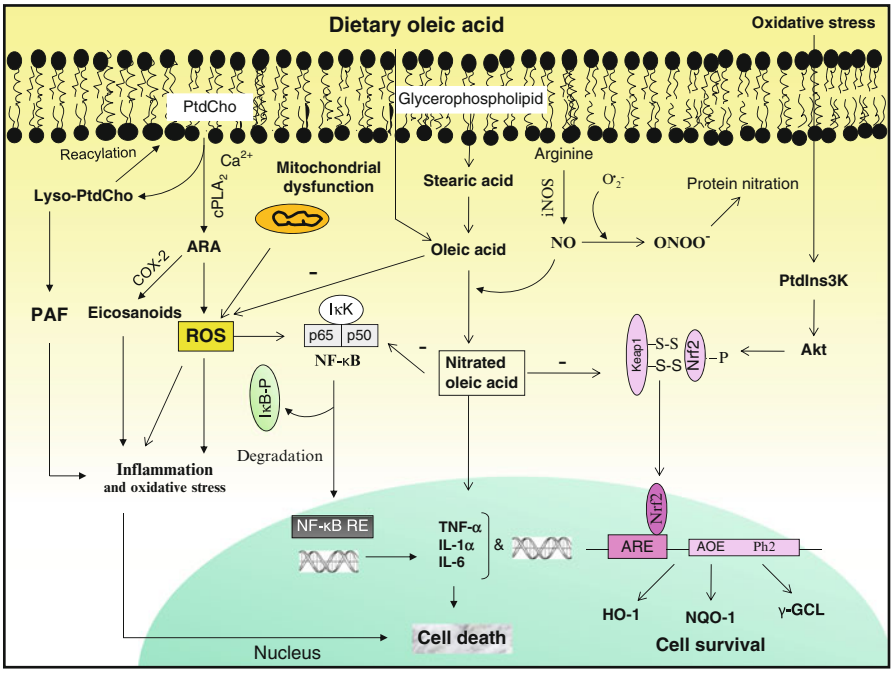

Fig. 2.8 Regulation of oxidative stress and inflammation along with modulation of NF-κB and NrF2 by nitrated oleic acid. Phosphatidylcholine (PtdCho); lyso-phosphatidylcholine (lyso-PtdCho); arachidonic acid (ARA); platelet-activating factor (PAF); cytosolic phospholipase A_2 ($cPLA_2$); cyclooxygenase-2 (COX-2); reactive oxygen species (ROS); nuclear factor kappaB (NF-κB); nuclear factor κB-response element (NF-κB-RE); inhibitory subunit of NF-κB (IκB); phosphorylated IκB (IκB-P); tumor necrosis factor-α (TNF-α); interleukin-1β (IL-1β); interleukin-6 (IL-6); inducible nitric oxide synthase (iNOS); superoxide (O_2^-); and NFE2-related factor 2 (Nrf2); heme oxygenase 1 (HO-1); NADH quinine oxidoreductase, γ-glutamylcystein ligase (γ-GCL)

with beneficial effects of olive oil still remain(s) speculative. This suggests that more studies are needed on the health benefits of olive oil.

2.2.3 Biochemical Effects of Olive Oil Phenolic Compound on the Brain

Most fatty acids enter the brain from the blood through blood–brain barrier (BBB), which is a complex cellular system formed by specialized endothelial cells that line cerebral capillaries, together with perivascular elements such as closely associated astrocytic end-feet processes, perivascular neurons, and pericytes. The primary function of the BBB is to create ionic homeostasis for neuronal and glial cells functions, supplement the brain with nutrients, and protect it from toxic insults by

sophisticated transport systems. Studies on the transport of [1-^{14}C]oleic acid in primary human brain microvessel endothelial cells (HBMEC) indicate that transport of oleic acid is increased significantly in the presence of bovine serum albumin (Mitchell et al. 2009). The inclusion of nonspecific fatty acid uptake inhibitor, phloretin significantly decreases [1-^{14}C]oleic acid uptake by HBMEC. Similarly, knocking down of fatty acid transport protein-1 or fatty acid translocase/CD36 significantly also decreases [1-^{14}C]oleic acid transport across the HBMEC monolayer from either apical as well as basolateral sides. These findings support the view that a fatty acid acceptor is also associated with the oleic acid transport across HBMEC monolayers (Mitchell et al. 2009). Thus, fatty acids (including oleic acid) enter brain through BBB as fatty acid/albumin complex, fatty acid transport protein-1, and to lesser extent from circulating lipoproteins. Acyl-CoA synthetases trap fatty acid by forming acyl-CoA, which cannot diffuse out of the cell. Selection and incorporation of fatty acid into phospholipids is controlled largely by enzymes of Lands cycle, which begins with the acyl-CoA synthetase (Farooqui et al. 2000; Hamilton and Brunaldi 2007). Albumin not only activates the sterol regulatory element-binding protein-1, but also upregulates stearoyl-CoA 9-desaturase mRNA (Tabernero et al. 2002; Polo-Hernandez et al. 2010). Furthermore, when the activity of sterol regulatory element-binding protein-1 is inhibited by the overexpression of a truncated form of this protein, albumin produces no effect on stearoyl-CoA 9-desaturase mRNA, indicating that the effect of albumin is mediated by this transcription factor. The stimulation by albumin can be prevented either by retarding traffic to the endoplasmic reticulum or adding albumin–oleic acid complex. In addition, oleic acid also induces the expression of microtubule associated protein-2 (MAP-2), a marker of dendritic differentiation (Rodríguez-Rodríguez et al. 2004; Polo-Hernandez et al. 2010). The time course of MAP-2 expression during brain development coincides with that of stearoyl-CoA desaturase, the limiting enzyme of oleic acid synthesis, suggesting that both phenomena coincide during development. The effect of oleic acid on MAP-2 expression is most probably independent of autocrine factors synthesized by neurons (Rodríguez-Rodríguez et al. 2004), and exogenous or endogenous oleic acid by astrocytes exerts its neurotrophic effect through a protein kinase C-dependent mechanism. This effect can be prevented by sphingosine or two myristoylated peptide inhibitors of protein kinase C (Rodríguez-Rodríguez et al. 2004). Thus, during brain development, the presence of albumin plays an important role by triggering the synthesis and release of oleic acid by astrocytes, which induces neuronal differentiation through its interactions with transcription factor NeuroD2 (Tabernero et al. 2001, 2002; Rodríguez-Rodríguez et al. 2004).

In developing rat brain, oleic acid is synthesized from stearic acid by astrocytes via stearoyl-CoA desaturase catalyzed reaction. It is released from astrocytes and utilized by neurons for the synthesis of neural membrane phospholipids. It specifically incorporates into growth cones. In developing brain, oleic acid promotes axonal growth, neuronal clustering, and expression of the axonal growth-associated protein-43 (GAP-43), indicating that this fatty acid facilitates neuronal differentiation. The effect of oleic acid on GAP-43 synthesis is mediated through the activation of protein kinase C (PKC) and is blocked by PKC inhibitors, such as H-7, polymyxin,

or sphingosine. The expression of GAP-43 is significantly increased when neurons are co-cultured with astrocytes in the presence of albumin (Tabernero et al. 2001; Polo-Hernandez et al. 2010).

Long-term consumption of refined- (ROO) and pomace- (POO) olive oil not only modulates brain fatty acid composition in apolipoprotein E (apoE) knockout (KO) mice, but also reduces the level of arachidonic and eicosapentaenoic acid, suggesting a decrease in the generation of pro- and anti-inflammatory eicosanoids (Alemany et al. 2009). The consumption of ROO and POO also influences the levels of pivotal membrane proteins implicated in the activation of PKA and PKC, supporting the view that ROO and POO produce positive effects on neuroinflammation and brain function. The combination of these two molecular effects might convert ROO and POO oils into valuable functional foods in diseases involving apoE deficiency (Alemany et al. 2009). The beneficial effects of olive oil on brain function are not only due to its antioxidative phenolic compounds, but also due to its high content of monounsaturated fatty acids, i.e., oleic acid (Perez-Jimenez et al. 2006), which has only one double bond, therefore an oleic acid-rich neural membrane will be less fluid than a membrane rich in linoleic acid, which has two double bonds. The main mechanism by which the components of olive oil modulate neural membrane and endothelial cell function involves inhibition and/or scavenging of ROS. Oleic acid and β-sitosterol may reduce intracellular ROS by creating a less-oxidant environment through inhibition of intracellular ROS production. β-Sitosterol may also enhance SOD activity, hence decreasing superoxide levels (González-Correa et al. 2007). In addition, oleuropein and oleanolic acid and minor components of olive oil may act directly on cyclooxygenases and lipoxygenases, which are inhibited at different points by phenolics and triterpenoids. Similarly, IL-1β expression is also inhibited by phenolic components of olive oil, contributing to neuroprotection and protection of endothelium against vasoconstriction, platelet aggregation, and monocyte adhesion (González-Correa et al. 2007).

In the brain, oleic acid is also converted into nitrated oleic acid. This metabolite is a highly reactive electrophilic compound that can modulate a variety of cellular targets, including thiol residues and peroxisome proliferator-activated receptor γ (Freeman et al. 2008; Jain et al. 2008; Trostchansky and Rubbo 2008). It is proposed that esterified nitrated fatty acids represent a sink of bioactive mediators, which are produced during nitrative stress leading to cellular dysfunctions after its release from the membrane by phospholipase A_2 (Jain et al. 2008). Free nitrated oleic acid is a stimulator of somatosensory and visceral nociceptors. It acts through the selective and direct activation of Transient Receptor Potential A1 (TRPA1) channels in a concentration-dependent manner (Taylor-Clark et al. 2009; Andersson et al. 2008). Although the role of nitrated oleic acid in neurodegenerative diseases is not fully understood, several studies indicate that 9- and 10-nitro-9-*cis*-octadecenoic acid is a potent ligand for peroxisome proliferator activated receptors (PPAR) at physiological concentrations (Taylor-Clark et al. 2009; Baker et al. 2005). PPAR-γ agonists prevent Aβ neurotoxicity in hippocampal neurons. In addition, based on concentration–response analysis in both neurons and hTRPA1-HEK cells, it is suggested that nitrated oleic acid is the most potent endogenous Transient receptor

potential cation channel, subfamily A1 (TRPA1) agonist. Oleoylethanolamide (OEA), the naturally occurring amide of ethanolamine and oleic acid interacts with peroxisome-proliferator-activated receptor alpha (PPARα), which is involved in feeding regulation and it has been proposed to play a role in sleep modulation (Soria-Gómez et al. 2010). The peripheral administration of OEA reduces food intake and increases waking with a concomitant reduction of rapid eye movement sleep. In addition, OEA treatment produces deactivation of the lateral hypothalamus, as inferred from the c-Fos expression and intralateral hypothalamus injections of OEA produce effects similar to the peripheral administration (Soria-Gómez et al. 2010). Oleic acid and OEA inhibit LPS-mediated production of NO and prostaglandin E_2 as well as expression of iNOS and COX-2 by blocking LPS-mediated NF-κB activation and phosphorylation of inhibitor κB kinase (IKK) in BV2 microglia (Oh et al. 2009, 2010). OEA inhibits LPS-mediated phosphorylation of Akt, p38 MAPK, and ERK; activation of PtdIns 3-kinase; and accumulation of reactive oxygen species (ROS). The effect of OEA can be blocked by AM630, a specific antagonist of the CB2 receptor. It is proposed that oleic acid and OEA show an anti-inflammatory effect through inhibition of NF-κB activation in LPS-stimulated BV2 microglia. Emerging evidence suggests that oleic acid, nitrated oleic acid, and OEA comprise a novel class of lipid mediators, which interact with various signal transduction pathways to modulate cell signaling. Although it is not known, but it is likely that their levels are altered in neurological disorders, which are accompanied not only by a higher degree of ROS and $NO^{\bullet}$ production, but also by diminished functions of mitochondria, endoplasmic reticulum, and the proteasome system, which are responsible for the maintenance of the normal protein homeostasis of neural cells (Moncada and Bolanos 2006; Farooqui 2009).

2.3 Effect of Oleic Acid on Neurological Disorders

With an increase in lifespan and changing population demographics, the incidence of neurological disorders is expected to increase significantly in the twenty-first century. The most challenging neurological disorders are neurodegenerative diseases, which are accompanied by age-related gradual decline in neurological function and characterized by neurodegeneration in specific area of the human brain (Farooqui 2010). Examples of neurodegenerative disorders include Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS). Although considerable information is available on potential mechanisms and pathology of neurodegenerative diseases, successful treatment strategies for neurodegenerative diseases have so far been limited because most available treatments are symptomatic and not directed towards the cause of neurodegeneration (Farooqui 2010). Most of neurodegenerative diseases are multifactorial and accompanied by oxidative stress, neuroinflammation, abnormalities in

immune system, BBB abnormalities, and accumulation of disease proteins, such as τ, β-amyloid in AD, α-synuclein in PD, and huntingtin in HD. The dysfunction of BBB is accompanied by the disruption of tight junctions, alterations in transport of molecules (plasma proteins) between blood and brain and brain and blood, aberrant angiogenesis, vessel regression, brain hypoperfusion, and changes in inflammatory responses. These processes may contribute to a "vicious circle" that leads to progressive synaptic loss and neurodegeneration in neurodegenerative diseases (Zlokovic 2008). A common feature of neurodegenerative diseases is a long course until sufficient protein accumulates, followed by a cascade of symptoms over many years with increasing disability leading to death (Jellinger 2009; Farooqui 2010).

Ingestion of olive oil not only modulates oxidative stress, with but also influences immune function, particularly the inflammatory processes associated with the immune system. Olive oil is a nonoxidative dietary component, and the attenuation of the inflammatory process by olive oil can be explained by its modulatory effects on oxidative and inflammatory stresses, which are closely associated with the pathogenesis of neurodegenerative diseases in man. The antioxidant effects of olive oil are probably due to a combination of its high oleic acid content (low oxidation potential compared with linoleic acid) and its content of a variety of plant antioxidants, particularly oleuropein, hydroxytyrosol, and tyrosol. The generation of nitrated oleic acid under nitrosative stress can inhibit neuroinflammation by blocking NF-κB activation and prevent oxidative stress by stimulating transcription factor NrF2. In addition, neuroinflammation in neurological disorders may elicit pain, which may be mediated by the activation of somatosensory and visceral nociceptive sensory nerves. Recently, a number of phytochemicals, such as allyl isothiocyanate, cinnamaldehyde, and phytocannabinoids have been shown to activate the transient receptor potential (TRP) ion channel family of receptors (TRPA1 receptors) (Bandell et al. 2004; De Petrocellis et al. 2008). Ingestion of olive oil and the synthesis of nitrated oleic acid may decrease the intensity of pain through the activation of nociceptive neurons via TRPA1 receptor-mediated process (Bautista et al. 2006). It is also possible that high oleic acid content and a proportionate reduction in linoleic acid intake would allow a greater conversion of α-linolenic acid (18:3n-3) to longer-chain n-3 PUFA, which may produce beneficial effects in neurodegenerative diseases (Farooqui 2009, 2010).

2.3.1 Beneficial Effects of Olive Oil Components in Alzheimer Disease

It is well known that AD is accompanied by dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe. Age is the most important factor that predisposes persons to the nonfamilial form of the disease. Brain from AD patient contains fewer synapses and reduced levels of synaptic proteins and neural membrane phospholipids (Farooqui 2010).

The two classical pathological hallmarks of AD include the deposition of aggregated Aβ peptide and neurofibrillary tangles (NFTs) composed of hyperphosphorylated τ protein, a microtubule (MT) associated protein, which fibrillizes and aggregates into neurofibrillary tangles. Multiple mechanisms, such as genetic mutations, posttranslational modifications, and intracellular environmental changes have been described to produce tau misfolding and fibrillization to form NFTs, which bear the properties of amyloid deposits (Lee et al. 2001). NFTs accumulation also occurs in tauopathies. Olive oil component, oleocanthal, the dialdehydic form of (-)-deacetoxy-ligstroside aglycone, inhibits tau fibrillization by interacting with the T40 and MT-binding region K18 of tau protein (Li et al. 2009). Using PHF6 consisting of the amino acid residues VQIVYK, a hexapeptide within the third repeat of tau that is essential for fibrillization, it is shown that oleocanthal forms adduct with the lysine residues via initial Schiff base formation and thereby inhibits tau fibrillization (Li et al. 2009). Based on detailed investigation using Fourier transform infrared (FTIR) spectroscopy, it is demonstrated that oleocanthal reacts with tau in the random coil form and prevents its conversion to the β-pleated sheet conformation. Structural activity studies of a series of oleocanthal analogues suggest that both aldehyde functional groups are essential for the inhibitory activity of oleocanthal (Li et al. 2009). Oleocanthal also inhibits the fibrillization of both Aβ40 and Aβ42 in vitro (Li et al. 2009). The similarities between the amyloidogenic proteins Aβ and tau in forming β-sheet strands and inhibition of fibrillization by oleocanthal further support the existence of a common mechanism of fibril formation. Other NSAIDs, including aspirin, naproxen, flurbiprofen, and indomethacin failed to block tau fibrillization at concentration up to 100 μM. Thus, the inhibitory effect of oleocanthal on tau fibril formation may represent a novel activity not shared by other NSAIDs (Li et al. 2009). It is also shown that oleocanthal has the capacity to alter the oligomerization state of β-amyloid (Aβ) oligomers while protecting neurons from the synaptopathological effects of Aβ. Thus, oleocanthal protects neurons from Aβ-induced synaptic deterioration (Pitt et al. 2009). Oleic acid also reduces secreted Aβ levels in amyloid precursor protein (APP) 695 transfected Cos-7 cells (Amtul et al. 2010). These findings are supported by results obtained in an early onset AD transgenic mouse model expressing the double-mutant form of human APP, Swedish (K670N/M671L) and Indiana (V717F) fed with a high-protein, low-fat (18 % reduction), cholesterol-free diet enriched with oleic acid. These mice have been reported to show an increase in Aβ40/Aβ42 ratio, reduced levels of β-site APP cleaving enzyme (BACE), and reduced presenilin levels along with reduced amyloid plaques in the brain. The decrease in BACE levels is accompanied by increase in levels of a nonamyloidogenic soluble form of APP (sAPPα). Furthermore, the low-fat/+OA diet produces an augmentation of insulin-degrading enzyme and insulin-like growth factor-II. These results support the view that oleic acid supplementation and cholesterol intake restriction in a mouse model of AD reduce AD-type neuropathology in early onset AD transgenic mouse model (Amtul et al. 2010).

2.3.2 *Beneficial Effects of Olive Oil Components on Hypoxic Injury*

Studies on the effect of olive oil components (Hydroxytyrosol) in a model of hypoxia–reoxygenation in rat brain slices indicate that hydroxytyrosol (5 and 10 mg/kg per day p.o.) reduces lactate dehydrogenase (LDH) efflux by 37.8 % and 52.7 %, respectively (González-Correa et al. 2008), supporting the view that this olive oil components modify processes related to thrombogenesis in brain hypoxic injury. These components reduce oxidative stress and modulate the inducible isoform of nitric oxide synthase, diminishing platelet aggregation, and protecting the brain from the effects of hypoxia–reoxygenation (González-Correa et al. 2007). Similarly, in the transient middle cerebral artery occlusion rat model (2 h of occlusion, 22 h of reperfusion), tyrosol treatment results in a dose-dependent neuroprotective effect (Bu et al. 2007). In an in vivo study of rat cerebral ischemia–reperfusion injury, oral administration of olive oil reduces infarct volume, brain edema, BBB permeability, and improves neurologic deficit scores after transient middle cerebral artery occlusion in rats (Mohagheghi et al. 2010).

2.3.3 *Beneficial Effects of Olive Oil Components on Atherosclerosis*

Atherosclerosis disrupts neuronal signaling pathways by altering lipid composition of neural membranes. This process may facilitate neuroinflammation and oxidative stress. Studies on the effect of refined olive oil (ROO) and pomace-(POO) olive oil in the brain of apolipoprotein E (apoE) knockout (KO) mice for 11 weeks indicate that incorporation of these oils increase the proportions of oleic acid neural membranes while levels of the saturated fatty acids (palmitic and stearic acid) are decreased (Alemany et al. 2010). This results in a higher MUFA:SFA ratio in apoE KO mice brain. Furthermore, both oils reduce the level of arachidonic and eicosapentaenoic acid, indicating a decrease in the generation of pro- and anti-inflammatory eicosanoids. In addition, refined olive oil and pomace olive oil increase the density of membrane proteins, implicating both the Gαs/PKA and Gαq/PLCβ1/PKCα signaling pathways (Alemany et al. 2010). The combined long-term effects of consumption of refined olive oil and pomace olive oil on neural membrane fatty acid composition and the level of signaling proteins associated with PKA and PKC activation suggest positive effects on neuroinflammation and brain function in apoE KO mice brain, and conversion of these oils into promising functional foods in diseases involving apoE deficiency (Alemany et al. 2010).

2.3.4 *Beneficial Effects of Olive Oil Components on Brain Tumor*

Astrocytomas are among the most common and aggressive type of primary malignant tumors in the neurological system lacking effective treatments despite the use of multimodal drug regimens. Studies on the effect of olive oil components (uvaol and erythrodiol) on the human 1321N1 astrocytoma cell line indicate that uvaol and erythrodiol inhibit 1321N1 cells proliferation in a time- and dose-dependent manner (Martin et al. 2009). This inhibition is associated with the induction of apoptosis. The effect of uvaol and erythrodiol on 1321N1 cells is accompanied by the appearance of apoptosis-specific hallmarks, such as redistribution of cells into the subdiploid phase of the cell cycle, translocation of phosphatidylserine to the outer leaflet of the cellular membrane, fragmentation of nuclei, and production of ROS, which are accompanied by the fall in $\Delta\Psi_m$ (Martin et al. 2009). Emerging evidence suggests that natural alcoholic triterpenes (uvaol and erythrodiol) are powerful inhibitors of cell growth and efficient apoptotic killing agents. These components can be used to develop the treatment of astrocytomas. Similarly, studies on the antitumoral effects of oleanolic acid and maslinic acid on human astrocytoma cell lines also indicate that oleanolic acid and maslinic acid inhibit DNA synthesis and induce apoptosis in human 1321N1 astrocytoma cells in a dose-dependent manner (Martin et al. 2007). This conclusion is based on typical apoptotic morphologic features, such as translocation of plasma membrane phosphatidylserine and activation of caspase-3 supporting the view that this type of cell death is caused by apoptosis.

2.4 Conclusion

The phenolic compounds of olive oil and oleic acid have bioavailability in humans. The high bioavailability of oleic acid and phenolic compounds lends support to the evidence that nitrated oleic acid and phenolic components exert beneficial effects on human health. Although the beneficial health effects of virgin olive oil ingestion are well known, it is only recent that the biological properties of nitrated oleic acid and olive oil phenolic compounds have been investigated. Olive oil phenolic compounds have been shown to beneficially alter lipid composition, platelet and cellular function, as well as reduce oxidative stress and neuroinflammation. Their beneficial effects are supported by the low rate of brain-related diseases among populations residing in the Mediterranean region. For example, the antiatherogenic effects of olive oil may explain the low rate of heart disease and stroke in Mediterranean populations. The anti-inflammatory effects that arise from the ingestion of olive oil phenolic compounds have been shown to provide protection against diseases marked by an inflammatory component. These biological properties may have a significant impact on population health through the reduction in incidence of chronic neurodegenerative disease development.

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