The Antidepressant Effect of Linseed and Olive Oils on Reserpine-Induced Depressed Male Albino Rats

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ABSTRACT

The present study aimed to investigate the antidepressant potential of linseed and olive oils on reserpine model of depression in male rats through their effects on the levels of monoamine neurotransmitters and behavioral changes induced by reserpine. This study was conducted on 60 male albino rats divided randomly into six main groups: the first is the control group that included normal rats; the second and third groups contained normal rats orally administrated with linseed and olive oils, respectively; the fourth or depressed group contained animals treated with reserpine (ip) alone; and the fifth and sixth groups included depressed animals treated orally with linseed and olive oils, respectively. Neurochemical monoamines such as serotonin, norepinephrine and dopamine were measured in cerebral cortex and hippocampal monoamine brain areas and Behavioral studies (immobility time) were measured to evaluate the antidepressant effect of both oils. The obtained results demonstrated that daily injection of rats with reserpine resulted in a significant elevation in the immobility time matched with a significant decrease in the cerebral cortex and hippocampal monoamine neurotransmitters levels; while daily treatment of the reserpinized rats with both linseed and olive oils returned significantly the decrease of both cortical and hippocampal monoamine neurotransmitters levels to approach the normal control values coupled with significant reduction in the immobility time. Results indicated that increased immobility time induced by reserpine was restored into normal control levels by linseed and olive oils treatment for 30 days. It could be concluded that the depression deterioration markers induced in rats by reserpine can be restored significantly by either linseed or olive oils via their antioxidant capacity as well as anti depressant potential of their constituents.

Key words: Reserpine, linseed oil, olive oil, depression, antioxidants.

Introduction

Mental depression is a chronic illness that affects a person’s mood, thoughts physical health and behavior and may range from a very mild condition, bordering on normality to severe depression, sometimes called “psychotic depression” accompanied by hallucinations and delusions (Dhingra and Sharma, 2006). Depression is a devastating and prevalent disease, with profound effects on neural structure and function. It is reported as one of the most common psychiatric disorder in outpatient clinic population and in subjects seen in various medical and surgical setting (Goswami et al., 2016). Major depressive disorder (MDD) is a recurrent, debilitating, and potentially life threatening illness. Depression is undoubtedly an extremely complex and heterogeneous condition (Logan, 2004). Depression is a leading cause of morbidity worldwide (Valuck et al., 2012); it is the main cause of suicide as about 70% of all suicides are attributed to untreated depression (Wong et al., 2000).

Several theories of depression do exist, including modulation of monoaminergic neurotransmission, alterations in neuroplasticity, and relation of hippocampus with depression are briefly mentioned in the review (Goswami et al., 2016). Antidepressants are widely used for treating major and minor depression (Hwang et al., 2008). Many antidepressant drugs are available with different pharmacological profiles from different classes: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) (Quintin and Thomas, 2004). There are some limitations with these drugs because there is a long delay before relief for symptoms, some patients with major depression are resistant to treatment, there is a risk to induce manic symptoms in patients with bipolar disorder (MDD) is a recurrent, debilitating, and potentially life threatening illness. Depression is undoubtedly an extremely complex and heterogeneous condition (Logan, 2004). Depression is a leading cause of suicide as about 70% of all suicides are attributed to untreated depression (Wong et al., 2000).

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disorders and these drugs have no effect on the psychotic symptoms frequently associated to major depression (Quintin and Thomas, 2004). Because drugs actually used in the treatment of depressive disorders need a longer duration to produce significant clinical effects or remain sometimes ineffective, there is a need to develop adjunctive therapeutic approaches that may help to hasten or to improve antidepressant effects (Venna et al., 2009).

Flaxseed (linseed) is derived from the flax plant (Linum usitatissimum), of the family Linaceae, which is cultivated worldwide for its fiber and oil (Dugani et al., 2008). Linseed oil containing essential fatty acids is cheap, plenty and highly used as edible oil in India, Asia and also in the western world but the oil is prone to oxidation (Bera et al., 2006). Linseed oil contains α-linolenic acid (ALA), linoleic acid (LA), palmitic acid and oleic acid (Vijaimohan et al., 2006) it contains ALA and LA with a ratio, known as the highest n-3/n-6 polyunsaturated fatty acids (PUFA) ratio amongst plant sources (National Research Council, 1993). Main physiological benefits of linseed oil are attributed primarily to the high ALA content (Burdge and Calder, 2005). Indeed, linseed oil is the main component of the linseed and has many beneficial functions to human health (Zhang et al., 2008). Moreover, Previous studies have proven that linseed oil has a positive effect on the minimization of many diseases such as hyperlipidemia (Vijaimohan et al., 2006), colon tumor (Dwivedi et al., 2005), mammary cancer (Chen et al., 2006) and atherosclerosis (Yamashita et al., 2005). Clinical conditions such as cardiovascular diseases (CVDs), blood pressure, cancer, skin diseases and immune disorders such as renal failure, rheumatoid arthritis (RA) and multiple sclerosis may be prevented by ALA in linseed oil (Kelley et al., 1991). Then-3 PUFAs in linseed oil have anti-inflammatory properties that are mediated by the production of anti-inflammatory eicosanoids (Cohen et al., 2005). ALA in linseed oil is ultimately converted to docosahexaenoic acid (DHA), a fatty acid important for the development of the infant brain and retina (Francois et al., 2003). Furthermore, n-3 PUFAs in linseed oil supplementation may be beneficial in the treatment of several psychiatric disorders, including depression (Antypa et al., 2009).

Also, olive oil is one of the main sources of dietary fatty acids. Olives and their oil contain oleic acid and a series of polyphenols (Montedoro et al., 1992). It is used since 4000 B.C. by the Mediterranean populations as a food, drug, and cosmetic as well as it has been the object of numerous epidemiologic, clinical, and experimental studies in the last few decades (Viola & Viola, 2009). Epidemiological studies suggest that the high consumption of the monounsaturated olive oil in Mediterranean countries is related with the low rates of CVDs and breast cancer as well as high life expectancy (Kiritsakis, 1999). It is clearly noted that the Mediterranean diet containing olive oil is associated with lower incidence of both coronary heart disease and certain tumors (Visoli and Galli, 1998). Olive oil, with its balanced fatty acid composition, is of high nutritional value; moreover, extra virgin olive oil, extracted from a fruit, has an important value related to the antioxidant power of minor components. In addition to that, the recommended ratio between n-3 PUFAs and n-6 PUFAs is found in olive oil, whereas the same cannot be said for other vegetable oils, with the exception of linseed and soy oils (Viola and Viola, 2009). The phenol components of olive oil have been shown to have a direct antioxidant action on skin, especially oleuropeine, which acts as a free radical scavenger at the skin level (Ancora et al., 2004).

Although olive oil consumption is believed to have a protective effect against other medical conditions, notably CVDs, the bibliographical evidence concerning a possible association with depression is only scant and indirect (Kyrozis et al., 2009). Low levels of monounsaturated fatty acids (MUFAs) were found in patients with recurrent depression (Assies et al., 2004). Also, significant negative correlations were observed between the degree of sleep disturbances and concentrations of oleic and palmitoleic acids in depressed patients (Irmsch et al., 2007).

Reserpine is a potent naturally occurring alkaloid derived from roots of several members of Rauwolfia genus (Doyle et al., 1955) and was one of the first psychopharmacological drugs to treat the psychiatric diseases and also as an antihypertensive (Bleuler and Stoll, 1955). It has been used clinically to control hypertension, schizophrenia, insomnia and insanity (Al-Bloushi et al., 2009). In later years, its use has been reduced because of precipitation of depression and extra pyramidal symptoms due to its central action (Sreemantula et al., 2004). Reserpine has the capability to deplete biogenic amines such as serotonin (5-HT), norepinephrine (NE) and dopamine (DA) (Metzger et al., 2002).

On light of the above mention, the objective of this study was to investigate the antidepressant action of linseed oil and olive oil on reserpine model of depression through their effects on the levels of monoamine neurotransmitters and behavioral changes induced by reserpine.
Methods:

Animals:

Sixty adult male Sprague Dawley rats (120-150g) were obtained from Animal House Colony of National Research Centre, Giza, Egypt. Animals were housed in stainless steel cages with ad libitum access to standard laboratory diet and tap water in temperature controlled (20-25°C), artificially illuminated (12hrdark/light cycle) conditions as well as room free of any chemical contamination. Animals were left, 10 days before the experiment, to acclimate with these conditions. All animals received human care in compliance with the guidelines of the Animals Care and Use Committee of National Research Centre (NRC), Giza, Egypt.

Induction of Depressed Animal Model by reserpine:

Reserpine (Laboratory Rasayan, Mumbai, India) was dissolved in a minimum amount of glacial acetic acid (1mg/µl) and then diluted to the appropriate volume (25 ml) with distilled water. Reserpine was injected interperitoneally (i.p.) to rats in a dose of (0.1 mg/kg b.w.) for 2 weeks to establish the animal model of depression according to Jancsar & Leonard (1983).

Experimental design:

After acclimation, animals were randomly divided into the following sex groups (10 rats each); the first group was comprised of normal animals i.p. injected with saline (2ml/animal/day) for 14 days and acted as control group; the second and third groups were comprised of normal animals administrated orally with linseed and olive oils respectively (2.5 g/kg/day) for a similar period; the fourth group contained animals injected (ip) with reserpine (0.1 mg/kg/day) for 14 days followed by saline (2ml/animal/day) administration for another 14 days and acted as untreated depressed group (Jancsar and Leonard, 1983); and the fifth and sixth groups contained depressed animals those received orally linseed and olive oils, respectively for a similar period.

Forced swim test:

Behavior despair was proposed as a model to test for antidepressant activity by Porsolt et al. (1977 & 1978). The procedure was essentially the same as described by Kulkarni and Mehta (1985). In brief, rats were forced to swim individually in a glass cylinder (height: 40 cm, diameter: 18 cm) containing fresh water of 23 cm height and maintained at 25°C (±3°C). After an initial 2 min period of vigorous activity, each animal assumed a typical immobile posture. A rat was considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The total duration of immobility was recorded during the next 4 min of a total 6 min test. The immobility durations were recorded for all animals and each animal was tested only once.

Brain (cerebral cortex and hippocampus) tissues sampling:

Following behavioral testing, rats were decapitated and their brains were quickly removed and rapidly transferred to an ice-cold Petri dish and dissected to obtain the hippocampus and the cerebral cortex according to Zeman & Innes (1963) and Glowinski et al. (1966). Each brain area was weighed and frozen at -80°C until analyzed.

Tissue homogenization:

To homogenizer tubes submerged in ice, acidified n-butanol was added (10 ml of the acidified butanol /gram tissue); brain samples should weigh at least 280 mg.

Determination of Monoamines Levels:

Quantitative estimation of cerebral corex and hippocampal monoamines neurotransmitters [serotonin (5-hydroxytryptamine; 5-HT), norepinephrine (NE) and dopamine (DA)] levels was carried out...
using spectrofluorometer (model Jasco-FP-777, Japan) according to the fluorometric method described by Ciarlone (1978).

**Statistical analyses:**

The obtained data were subjected to one way analysis of variance (ANOVA), followed by post hoc test, LSD at p≤0.05 using SPSS software program.

**Results**

The obtained results revealed that oral administration of rats with either linseed or olive oils (2.5gm/kg) for 30 days didn't significantly change the immobility time of FST; while daily injection (i.p.) of reserpine (0.1 mg/kg) for 45 days resulted in a significant increase (20.34%) when these groups were compared to the immobility time of normal rats.

Moreover, daily oral treatment of reserpinized rats with linseed or olive oils resulted in a significant decrease (-68.48% & -68.08%, respectively) in the duration of immobility time of the forced swimming test with reference to reserpinized rats. The immobility time of both groups was close to that of normal group reflecting their ameliorating potential (Table 1).

**Table 1:** Effect of daily oral administration of linseed and olive oils on the duration of immobility time (seconds) in the rat forced swimming test on reserpinized rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>Immobility Time (Seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (control) rats</td>
<td>71.76 ± 10.1(^B)</td>
</tr>
<tr>
<td>Reserpinized</td>
<td>217.72 ± 22.7(^A)</td>
</tr>
<tr>
<td>Reserpinized + linseed oil</td>
<td>68.62 ± 9.39(^B)</td>
</tr>
<tr>
<td>Reserpinized + olive oil</td>
<td>69.50 ± 11.85(^B)</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± standard error.

**Table 2:** Effect of daily oral administration of linseed and olive oils on the monoamine neurotransmitters [serotonin (5-HT), norepinephrine (NE) and dopamine (DA)] concentration in the cerebral cortex of normal and reserpinized rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serotonin (5-HT) (µg/g tissue)</th>
<th>Norepinephrine (NE) (µg/g tissue)</th>
<th>Dopamine (DA) (µg/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (control) rats</td>
<td>0.56 ± 0.05(^A)</td>
<td>2.5 ± 0.19(^A)</td>
<td>0.27 ± 0.01(^A)</td>
</tr>
<tr>
<td>Linseed oil treated rats</td>
<td>0.56 ± 0.08(^A)</td>
<td>2.4 ± 0.18(^A)</td>
<td>0.26 ± 0.01(^A)</td>
</tr>
<tr>
<td>Olive oil treated rats</td>
<td>0.56 ± 0.05(^A)</td>
<td>2.6 ± 0.24(^A)</td>
<td>0.29 ± 0.01(^A)</td>
</tr>
<tr>
<td>Reserpinized</td>
<td>0.34 ± 0.02(^B)</td>
<td>1.0 ± 0.13(^B)</td>
<td>0.18 ± 0.01(^B)</td>
</tr>
<tr>
<td>Reserpinized + linseed oil</td>
<td>0.53 ± 0.08(^A)</td>
<td>1.6 ± 0.08(^B)</td>
<td>0.25 ± 0.01(^A)</td>
</tr>
<tr>
<td>Reserpinized + olive oil</td>
<td>0.52 ± 0.05(^A)</td>
<td>1.9 ± 0.11(^B)</td>
<td>0.29 ± 0.02(^A)</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± standard error.

In reference to reserpinized rats, the daily oral treatment of reserpinized rats with linseed and olive oils for 30 days induced a significant increase in the cortical 5-HT, NE and DA levels[55.88% &52.94% for 5-HT; 51.96% &86.27% for NE; 38.89% & 61.11% for DA, respectively]. On the other hand, in comparing to normal control rats there is no significant change in the cortical 5-HT and DA concentrations [-5.36% & -7.14% for 5-HT; -7.4% &7.41% for DA, respectively], while the concentration of the cortical NE is still showing a significant decrease [-37.75% &-23.69%, respectively].

In the hippocampus of normal animals those were treated with linseed oil for 30 days, the three neurotransmitters (5-HT, NE and DA) showed non-significant change [7.3% ;7.88% & -5.15%,
Dosing might be sufficient for evaluating its efficacy since the effects of granules (that VMATs are involved in the presynaptic packaging of monoaminergic neurotransmitters into storage protein, thereby disrupting storage of catecholamines (DA and NE) and 5-HT; thirdly, reserpine blocks vesicular monoamine transporter 2 (VMAT2) resulting in depletion of monoamines; and it is well known that VMATs are involved in the presynaptic packaging of monoaminergic neurotransmitters into storage granules (Lohoff et al., 2008). In addition, it is important to note that partial compliance with reserpine dosing might be sufficient for evaluating its efficacy since the effects of reserpine in irres...
destabilizing central nervous system (CNS) vesicle membranes persists for a prolonged period of time (Giachetti and Shore, 1978).

The significant increase in the immobility time in FST as a consequence of daily injection of reserpine in compare to either control or linseed and olive oils treated animals goes in hand with the finding of Antkiewicz-Michaluk et al. (2014) and Gao et al. (2016).

Additionally, Leith and Barrett (1980) had been demonstrated, in an animal study, that increased immobility time in FST as a consequence to reserpine represented a condition similar to human depression which is amenable to be reversed by antidepressant drugs.

The recorded significant increase in the immobility time induced by reserpine in FST reflected a state of depression that was mediated by the parallel decrease in the monoamine levels in the cortex and hippocampus of rat brain.

The present data showed that oral treatment of depressed or reserpinized rats with linseed oil for 30 days resulted in a significant reduction in the immobility time in compare to its level of the depressed animal group; this reduction was close to the its level of normal rats. These mentioned results were in agreement with the study of Carlezon et al.(2005) and Shah et al. (2014) who reported that dietary supplementation with omega-3 fatty acids reduced immobility time in the FST when given for 30 days, but not for 3 or 10 days. Furthermore, the major finding of Huang et al.(2008) study is that the dietary supplement of omega-3 fatty acids attenuated the elevated immobility time and disturbed behaviors of swimming and climbing in the FST of the depressed rats.

The ability of linseed oil (rich in omega-3 fatty acids) to ameliorate the immobility time in the FST that concomitant with the normalization of the reserpine-induce deterioration in the monoamine levels both in cortex and hippocampal brain regions may reflect the antidepressant role of linseed oil.

Similarly, the present data showed that oral treatment of depressed or reserpinized rats with olive oil for 30 days resulted in a significant reduction in the immobility time in compare to its level of the depressed animal group. This effect is inconsistent with the (Perveen et al., 2013).

It was previously suggested by Sugiuara et al. (1996)that oleic acid (from olive oil) can be readily biosynthesized into oleamide. Akanmu et al. (2007) study showed that oleamide possessed an obvious antidepressant-like effect at dose of 10 mg/kg as it significantly decreased the immobility time and increased swimming behavior in FST. Linseed oil which is a source of the parent omega-3 polyunsaturated fatty acid, α-linolenic acid, was reported to improve at various dosages the symptoms of bipolar depression and agoraphobia (Rudin, 1981). The increment in monoamines (5-HT, NE and DA) in both cerebral cortex and hippocampal brain regions of reserpinized rats after treatment with linseed oil supplementation may be attributed to that linseed oil is the primary vegetarian dietary omega-3 polyunsaturated fatty acids source, and is the precursor to cellular membrane phospholipid eicosapentaenoic acid and docosahexaenoic acid (Rao et al., 2007).

A large amount of experimental arguments is now assessing relationships between n-3 PUFAs and monoaminergic neurotransmission (Chalon, 2006). N-3 PUFAs are essential components of the CNS neuronal membranes and are implicated in their dynamic structure, changing their fluidity (Sanchez-Villegas et al., 2007). It was stated that higher n-3 PUFAs concentrations lead to increased membrane fluidity, consecutively increase 5-HT transport (Fernstrom, 1999). Thus, these fatty acids have an effect on receptor function, neurotransmitter reuptake and on signal transmission (Sanchez-Villegas et al., 2007). Furthermore, n-3 fatty acids were proved to facilitate the production of 5-HT in animal experiments (Irmisch et al., 2007).

The improving influence of n-3 PUFAs on dopaminergic function was confirmed by many studies (Innis and Owens, 2001; Takeuchi et al., 2002). However, the precise mechanisms linking the supply of n-3 PUFAs and DA neurotransmission remain to be elucidated and are probably complex and multifactorial (Kodas et al., 2004). The mammalian brain is particularly rich in DHA (the main n-3 PUFAs) which is important for maintaining normal brain structure and function (Vancassel et al., 2008 and Innis, 2003) as it cannot be synthesized de novo in mammalian tissue, but must be obtained directly from the diet or by elongation from its shorter-chain nutritionally essential precursors, including 18:3n-3; ALA (Sprecher, 2000). Dietary DHA supplementation is reported to increase rat brain acetylcholine, NE, 5-HT and DA (Aid et al., 2003). Moreover, Hibbeln & Salem (1995) postulated that the 5-HT turnover rate in the CNS may be modulated by DHA which is a critical component of synaptic membranes (Salem, 1989). It was found that DHA deficiency is associated with dysfunctions of neuronal membrane stability and transmission of 5-HT, NE and DA, which might connect to the aetiology of mood and cognitive dysfunction of depression (Su, 2009).
In agreement with our results (Venna et al., 2009) observed antidepressant-like effects after using a diet consisting of a high proportion of n-3 PUFAs to treat depression and they reported that these antidepressant-like effects may be the result of interactions between PUFAs and 5-HT, NE or DA pathways. Indeed, it had been discussed that changes in fatty acids following chronic n-3 deficiency or enriched diet feeding may modify serotonergic and dopaminergic neurotransmission as well as may induce changes in 5-HT2 and D2 receptors (Delion et al., 1997). One possible explanation of the improvement of neurotransmission may be a consequence of synaptogenesis; N-3 PUFAs are able to modulate the expression of numerous genes in the brain including some of those governing synaptic plasticity (Kitajka et al., 2002). Using synaptophysin, a marker of synaptic density and synaptic vesicles formation Venna et al. (2009) confirmed this explanation when they demonstrated that chronic n-3 PUFAs supplementation was able to enhance synaptogenesis in the whole brain, especially in the hippocampus.

Also, the main finding of Vancassel et al. (2008) study was that supplementation with n-3 PUFAs seemed to have a reversing effect on the reduced 5-HT levels that were induced by the unpredictable chronic mild stress (UCMS). Although this "reversal effect" was proven for 5-HT levels, it was less clear for NE. For DA and metabolites; it was also difficult to observe clear effects of the n-3 PUFAs supplementation on the consequences of stress. However, many investigators have reported relations between n-3 PUFAs and the CA-related phenomenon (Hamazaki et al., 2005). Several lines of evidence have supported the notion that the 5-HT system modulates brain NE neurons (Haddjeri et al., 1997; Kaehler et al., 1999). So, it might be hypothesized that n-3 PUFAs influence serotonergic neuron activity that modulates NE neurons (Hamazaki et al., 2005). Moreover, in the frontal cortex, Chalon et al. (1998) measured monoaminergic neurotransmission in rats following administration of a high n-3 PUFAs diet. Increased levels of both endogenous DA and D2 receptors were evident.

As there is substantial evidence supporting the correlation between low essential fatty acids and depression (Williams et al., 2006) and western population tend to be deficient in n-3 fatty acids (Hibbeln, 1998), n-3 supplementation can promote a strategy to mitigate depression (Ferraz et al., 2008). Moreover, Ferraz et al. (2008) demonstrated that when the window of supplementation was from post-natal day 21 until adulthood the fatty acids n-3 had a beneficial effect on preventing the development of depression-like behavior.

In terms of intervention, there are now several studies supporting n-3 PUFAs supplementation as having a distinct antidepressant role (Parker et al., 2006) and preliminary results of randomized controlled trials suggest that an additional intake of n-3 PUFAs (0.5-9.6 g/d) leads to a greater reduction in depressive symptoms compared with standard treatment in depressed patients (Stoll et al., 1999; Su et al., 2003). Furthermore, there is a strong evidence supports the use of n-3 PUFAs in the treatment of mood disorders with approximately 1-2 g/day of n-3 PUFAs appearing to be effective (Ross et al., 2007).

Keeping on our results, an open-label study reported that linseed oil (a daily dose of 0.1-0.5 gm of ALA/Kg of body weight, or 2-6 tablespoons) showed potent antidepressive properties in two out of three lithium-responsive patients with unipolar depression (Rudin, 1981).

Although in many clinical studies, n-3 PUFAs reportedly have beneficial effects in major depression (Peet and Horrobin, 2002; Su et al., 2003) some others opposed that (Marangell et al., 2003; 2004).

The present study demonstrated that olive oil supplementation produced significant increase in 5-HT, NE and DA in both cerebral cortex and hippocampus of reserpinized animals. The major component of olive oil is oleic acid (Nojima et al., 2007) which is the primary omega-9 fatty acid in the human diet and is the predominant monounsaturated fatty acid (MUFA) in olive oil (Wolfe et al., 2009). Published research supports the notion that oleic acid (from olive oil) can be readily biosynthesized into oleamide (Sugiura et al., 1996), a lipid which can induce sleep, increase pain thresholds, alter 5-HT receptors to enhance binding, alter food intake, and limit seizure potential (Martinez-Gonzalez et al., 2004). Oleamide is an endogenous fatty acid primary amide that possesses sleep-inducing properties in animals and that has been shown to affect serotonergic receptor responses and block gap junction communication (Boger et al., 1998).

The potential of oleamide to modify serotonergic neurotransmission in vivo is of great interest (Thomas et al., 1999). The endogenous synthetic pathways of oleamide are not known; however, its degradative enzyme, fatty acid amide hydrolase, which converts oleamide to oleic acid, was recently cloned from rat, mouse, and human tissues (Giang and Cravatt, 1997). Oleamide has diverse biological activities, including sleep induction and signaling modulation of several 5-HT receptor subtypes (5-HT1A, 5-HT2A/2C, and 5-HT7). The 5-HT7 receptor is predominantly localized in the hypothalamus, hippocampus and frontal cortex (Hedlund et al., 1999). Furthermore, the actions of oleic acid seem to be highly selective for 5-HT7 and also seem to allosterically modulate 5-HT7A to enhance its high-affinity.
agonist binding (Alberts et al., 2001). Furthermore, Wolfe et al. (2009) reported that diet rich in omega-9 fatty acids is associated with reduced likelihood of severe depression mood; and also Akanmu et al. (2007) suggested that oleamide has antidepressant-like property.

Oleamide has been reported to affect other systems such as gap junction, GABAergic, dopaminergic and serotonergic transmission (Akanmu et al., 2007); this suggests a wide range of its effects on CNS (Akanmu et al., 2007). Moreover, Oleamide has been reported to act on both the DA receptors (D₁ and D₂) on which the result of ligand binding are opposite to each other, that is, a stimulation and an inhibition of adenylate cyclase on D₁ and D₂, respectively (Katzung, 2001). Akanmu et al. (2007) also demonstrated that oleamide may be having affinity for both the dopamine D₂-like receptors and the D₁-like receptors.

It was found that patients with depression are under increased oxidative stress and that oxidative stress is associated with severity of depression (Tsuboi et al., 2004). Micro-constituents from virgin olive oil were shown to have antioxidant properties and capacities to improve endothelial function (Perez-Jimenezet al., 2005). González-Correa et al. (2007) found that olive oil is effective in reducing oxidative stress; these beneficial effects have been attributed, at least in part, to the phenolic compounds of olive oil, such as oleuropein and hydroxytyrosol. Moreover, olive oil provides monounsaturated fatty acids, which are not readily oxidizable (Moreno et al., 2001). In particular, olive oil is a source of at least 30 phenolic compounds (Tuck and Hayball, 2002) those are strong antioxidants and radical scavengers (Visserset al., 2004). The antioxidant polyphenolic chemicals in olive oil have been reported to have neuroprotective properties (Batino and Soledad-Ferreiro, 2004) and MUFAs from olive oil have a role in maintaining the structural integrity of neuronal membranes (Panza et al., 2004).

Tyrosol and hydroxytyrosol, the major olive oil phenolic compounds present in olive oil assamble forms or conjugates (Owen et al., 2000). Hydroxytyrosol may contribute to the antioxidant activities and other beneficial effects of extra virgin olive oil (Grignaffini et al., 1994). Hydroxytyrosol is also known as an endogenous metabolite of DA (Hashimoto et al., 2004). In fact, homovanillic acid, one of the main metabolites of DA, has also been reported as a major metabolite of hydroxytyrosol (Caruso et al., 2001).

Hashimoto et al. (2004) clearly demonstrated the protective role of hydroxytyrosol from olive oil against oxidative stress-induced cell damage in dopaminergic neurons. Oi-Kano et al. (2007) demonstrated that an extract of the phenolic fraction from extra virgin olive oil enhances NE and epinephrine secretions. In addition, oleuropein which is the pungent principle of olives and is found in extra virgin olive oil and in its aglycone form is reported by Oi-Kano et al. (2008) to be responsible for the enhancement of NE and epinephrine secretions. Briefly, if a beneficial effect of MUFAs and olive oil against depression exists, it could be mediated through several mechanisms, such as enhanced binding of 5-HT to its receptors, biosynthesis of the sleep-inducing substance oleamide and antioxidant properties of polyphenolic substances present in olive oil (Logan, 2005).

References


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