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Fennel Oil Treatment Mimics the Anti-Depressive and Anxiolytic Effects of Fluoxetine without Altering the Serum Cholesterol Levels in Rats

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TP was the Principal Investigator. SE, SA and ZB designed the experiments and wrote the manuscript. SY, SS and SQ conducted the experiments and analyzed the data. SH critically evaluated various versions of the manuscript.

Key words
Anxiety, Depression, Fennel oil, Fluoxetine.

ABSTRACT

Synthetic antidepressants are effective drugs for the treatment of psychiatric disorders. Along with the effectiveness these drugs are also associated with some side effects. Since ancient times herbs are used as medicinal purposes. One such herb is Fennel (*Foeniculum vulgare*). Fennel has many efficacious uses. It is a common herb and spice. It is used in many culinary purposes and also it has therapeutic purposes. In the present study antidepressant effects of fennel oil was monitored by comparing it with a synthetic antidepressant drug, fluoxetine. The rats were divided into three groups as control, drug and oil which were respectively treated with water, fluoxetine (0.3 mg/kg) and fennel oil (0.5 ml/day). The treatment was continued for three weeks. Struggling time in forced swim test (FST), number of square crossed in open field test (OFT) and time spent in open arm in elevated plus maze (EPM) was monitored weekly. Repeated administration of fennel oil for 3 weeks showed significant antidepressant- and anxiolytic-like effects in FST and EPM, respectively which were comparable to fluoxetine treated group. A significant increased cholesterol levels were observed in fluoxetine treated rats which was not observed in fennel oil treated rats. Therefore, repeated administration of fennel oil may exert antidepressive- and anxiolytic-like behaviors. These effects were found to be comparable to that of the clinically used synthetic drug, fluoxetine.

INTRODUCTION

The word depression is used in everyday language. Depression with 16% and anxiety with 10% of lifetime prevalence around the world are among the most common psychiatric disorders (Kessler *et al*., 2014). Brain is susceptible to the damaging effects of free radicals resulting in oxidative stress. Hence, oxidative stress has been implicated in the pathogenesis of psychotic illnesses (Berk *et al*., 2011). Treatment with antioxidant compounds has shown to ameliorate deleterious pathological conditions (Karabulut-Bulan *et al*., 2016). It is suggested that plant-derived antioxidants may provide therapeutic protection by increasing the antioxidant levels and normalizing the damage caused by oxidative stress which further protect against neuronal damage and may result in diminution of depression and anxiety symptoms (Lee *et al*., 2013; Xu *et al*., 2014).

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Herbs are used as folk medicines since times. Among many herbs *Foeniculum vulgare* mill has enduring therapeutic antiquity. *F. vulgare* mill belongs to Apiaceae family, it is umbelliferous and perennial herb (García-Jiménez *et al*., 2000). It is odoriferous and savory herb with many medical and nutritive uses (Barros *et al*., 2010). Phytochemical studies on *F. vulgare* revealed the presence of essential fatty acids, phenolic components, volatile compounds, and secondary metabolites. Most of these phyto-components are present in essential oil (Badgujar *et al*., 2014). Plant-derived phenolic compounds have shown multiple functions including reduction potential and act as hydrogen-donating antioxidants and free radical quenchers (Lee *et al*., 2000, 2001). The major constituent of essential oil of *F. vulgare* is trans-anethole (60-90%). Fennel oil also contain other minor constituents such as limonene (0.1–21.5%), (E)-phytol (0.1–6.0%), neophytadiene (0–10.6%), exo-fenchyl acetate (0.3– 3.8%), estragole (0.1–2.5%), and fenchone (0.1–3.1%) (Senatore *et al*., 2013). Approximately 12% of 1,8-cineole, 5% linalool, and 4% α-terpineol have also been reported in fennel oil (Mansour *et al*., 2011). In alternative medicine it is used as a diges-

tive, diuretic, lactagoge and carminative agent (Bilia *et al*., 2000). Pharmacological studies showed antibacterial, antioxidant, antithrombotic, antihepatotoxic, relaxant, analgesic and anti-inflammatory activities in various *in vitro* and *in vivo* paradigms (Rather *et al*., 2016). Antifungal, antiviral, and antiprotozoal activities have also been reported previously (Dua *et al*., 2013). Some of the publications stated that *F. vulgare* has chemopreventive, cytoprotective, hypoglycemic, antitumor, and oestrogenic activities (El-Soud *et al*., 2011; Pradhan *et al*., 2008; Oktay *et al*., 2003; Özbek *et al*., 2003). The essential oil of *F. vulgare* has been attributed to produce these pharmacological effects (Özbek *et al*., 2003). It is suggested that the synergistic effects of major and minor compounds of essential oil have significant role in various pharmacological activity (Badgujar *et al*., 2014).

Previous studies have examined the effects of fennel oil on peripheral system; however, studies regarding the beneficial effects on psychological behaviors are sparse. Previously, antidepressant and anxiolytic effects of fennel oil have been reported from our lab (Perveen *et al*., 2014). This study was designed to compare the effects of repeated administration of fennel oil with conventionally used antidepressant *i.e.,* fluoxetine on depression and anxiety-like behaviors in healthy adult rats. Prolong use of synthetic antidepressants such as specific serotonin reuptake inhibitor (SSRIs) has been associated with metabolic disturbances. Weight gain, increased serum cholesterol levels and increased body mass index have been reported previously due to the long-term use of SSRIs (Beyazyüz *et al*., 2013). Therefore, in this comparative study serum cholesterol levels were also measured following the administration of fennel oil and fluoxetine for three weeks.

MATERIALS AND METHODS

Experimental protocol

Animals were purchased from Agha Khan University animal house, Karachi, Pakistan, with an average weight of 200-250 g. To avoid the effect of social interaction, animals were housed individually with *ad libitum* access to cubes of standard rodent diet (4.47 kcal/g; containing 25% fat, 50% carbohydrate, and 25% protein) and tap water under a 12:12 h light/dark cycle (lights on at 7:00 AM) at controlled room temperature (22±2°C). Twenty four rats were divided into control, drug (fluoxetine) and fennel oil treated groups. Fluoxetine was purchased from Chemical Co. (St. Louis, USA) and fennel oil was purchased from local super market. 0.3 mg/kg of drug and 0.5 ml/day fennel oil (Perveen *et al*., 2014) was given orally to the drug treated rats and oil treated groups respectively for three weeks, whereas, controls were treated with tap water for the same period of time. Rats were subjected to forced swim test (FST), open field test (OFT) and elevated plus maze (EPM) test on 7th, 14th and 21st day of treatment to assess the depressogenic and anxiogenic behaviors. All experiments were carried out between 10:00 AM and 5:00 PM in a balanced design to avoid influence of order and time. The experimental procedures were performed in strict accordance with National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). All efforts were made to reduce animal suffering and to minimize the number of animals used in the experiments.

Behavioral assessment

Forced swim test (FST)

The FST is commonly used as standard pharmacological model for evaluating depression-like symptoms in rats (Porsolt *et al*., 1977). The dimensions of the apparatus and method used in the present study were same described previously (Haider *et al*., 2015). Briefly describing when the rats are placed in an inescapable chamber which is filled with water then the development of the state of immobility reflects the cessation of persistent escape directed behavior. In this test the animal's swimming behavior was monitored which can be defined as movement throughout the swim chamber (glass tank). In the present test immobility time was monitored. Struggling time was calculated by subtracting the immobility time from total time (300 s). The animal considered as immobile when it made no further attempts to escape and only tried to keep its head above the water.

Open field test (OFT)

The apparatus dimensions were same as mentioned by Haider *et al*. (2015). Rats were allowed to explore an open arena for 5 min. Apparatus consisted of 25 equal squares on the floor and number of squares crossed by each animal was recorded during the allocated time to monitor the exploratory activity.

Elevated plus maze (EPM) test

The dimensions of apparatus and method were same as described previously (Naqvi *et al*., 2012). Being the nocturnal animal, rat feels fear from elevated and open area therefore time spent in open arm of EPM was recorded to monitor the anxiety-like behavior. Significant increased time spent in open arm was taken as an index of anxiolytic effect of treatment.

Serum cholesterol estimation

Estimation of cholesterol level in serum was done by Zalatkis method (Nagórna-Stasiak, 1987).

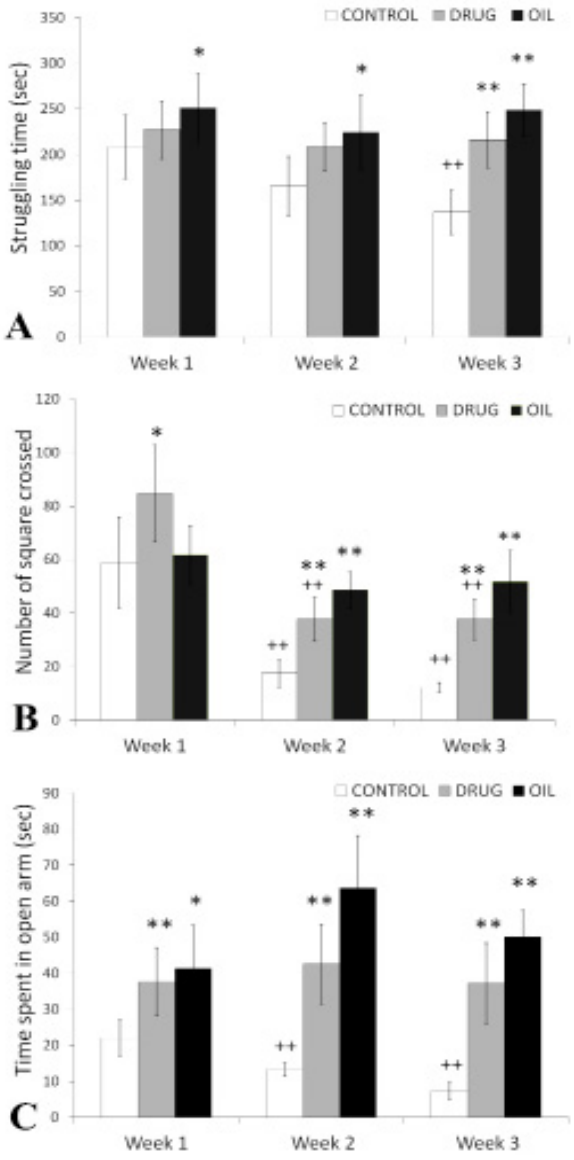

Fig. 1. Comparative effects of fluoxetine and fennel oil rats was assessed by forced swim test (A), open field test (B) and elevated plus maze (C). Values are means±SD (n = 8). Significant differences by Bonferroni test: *p<0.05, **p<0.01 from respective control animals; +p<0.05, ++p<0.01 from week one values of similarly treated animals following two-way ANOVA repeated measure design.

Statistical Analysis

Results are represented as Mean±SD. Data of behavioral testing were analyzed by two-way ANOVA with repeated measure design with Bonferroni test to compare the different groups. One-way ANOVA was used to analyze serum cholesterol levels followed by Tukey's post-hoc test. p>0.05 was considered to be non-significant.

RESULTS

The comparative effects of standard antidepressant drug and fennel oil administration in FST, OFT and EPM test are shown in Figure 1. Data for FST, which was analyzed by two-way ANOVA with repeated measure design, revealed significant effect of treatment [F(2,21)=23.3, p<0.01], weeks [F(2,42)=7.58, p<0.01] and significant interactions between treatment × weeks [F(4,42)=878.39, p<0.01]. In the present study rats were subjected to FST weekly during the treatment. It was observed that the rats treated with water showed gradual decrease in struggling time which was significantly reduced on third week as compared to that of first week (p<0.01). This pattern of struggling time was not observed in drug treated rats (p>0.05) because of its anti-depressant effects. The same pattern of drug was also observed in fennel oil treated rats. When the fennel oil treated rats were compared with controls, a significant increase in struggling time was observed indicating the potential anti-depressant like effects of fennel oil.

Data for OFT was also monitored by two-way ANOVA with repeated measure design. There was significant effect of treatment [F(2,21)=21.67, p<0.01], weeks [F(2,42)=59.75, p<0.01] and significant interaction between treatment × weeks [F(4,42)=6.33, p<0.01]. Post-hoc analysis by Bonferroni test revealed a significant decrease in exploratory activity in water treated rats with weekly exposure to OFT. Second and third week activity in these rats were significantly lower as compared to that of first week activity (p<0.01). Drug treated animals showed significantly increased activity as compared to that of controls (p<0.01) in all three weeks. But the gradual decrease in exploratory activity on second and third week was also observed in standard drug treated animals as compared to that of first week activity (p<0.01). Rats treated with fennel oil also showed significantly increased OFT activity during second and third week as compared to that of controls (p<0.01). Whereas in contrast to controls and drug treated animals, the fennel oil treated rats showed persistent exploratory activity in all three weeks showing the anti-depressant potential of fennel oil.

Analysis of data for EPM by two-way ANOVA with repeated measure design revealed significant effect of treatment [F(2,21)=111.4, p<0.01], weeks [F(2,42)=6.99, p<0.01] and significant interactions between treatment × weeks [F(4,42)=8.53, p<0.01]. Rats were exposed to the EPM weekly during the treatment in this study. The rats treated with water showed gradual decrease in time spent in open arm which was significantly reduced on second and third week as compared to the activity observed in first week (p<0.01). Standard drug treated (p>0.05) and fennel oil (p>0.05) treated rats did not exhibit reduced time spent

in open on repeated exposure. Moreover, standard drug as well as fennel oil administration showed significant increased time spent in open arm as compared to that of controls on weekly exposure demonstrating the anti-anxiety potential of fennel oil administration.

The serum cholesterol levels were also measured following the administration of synthetic drug and fennel oil. One-way ANOVA revealed significant effects of treatment [$F(2,21)=7.164$, $p<0.01$]. Three weeks administration of drug significantly increased cholesterol level as compared to controls ($p<0.01$) whereas, this increase in cholesterol levels were not observed in fennel oil treated rats (Fig. 2).

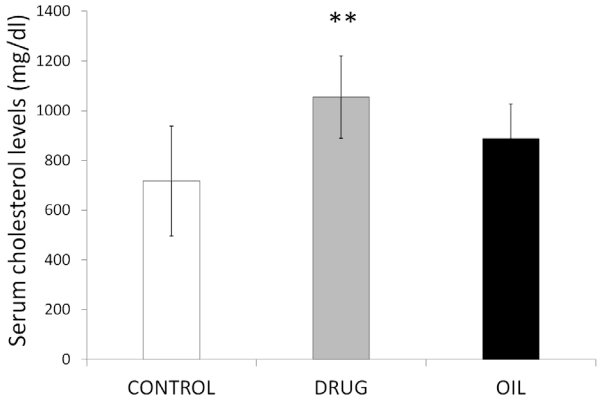

Fig. 2. Effects of fluoxetine and fennel oil administration for three weeks on serum cholesterol levels. Values are means±SD (n = 8). Significant differences by Tukey's post-hoc test: **$p<0.01$as compared to controls following one-way ANOVA.

DISCUSSION

Depression is the most common widespread forms of psychopathology, characterized by variety of symptoms like hopelessness, relationship problems, fatigue, lack of energy, inability to experience happiness in life and many other dramatic changes are observed in depressed individual that vary with the severity as well. In medicinal science the role of certain food and food components have found to have beneficial physiological and psychological effects (Everitt *et al*., 2006).

It is previously reported that depression slow downs the normal activities of individuals (Aswar *et al*., 2017). For this purpose we used forced swim test to measure the antidepressant activity following fennel oil administration on animal behavior. The results of our present study showed that the drug (fluoxetine) increased the struggling time of animal in all 3 weeks and this increase in struggling time was also observed in rats administrated with fennel oil as compared to that of controls. This antidepressant effects following the administration of standard antidepressant and fennel oil were also observed in OFT paradigm. Another parameter *i.e.,* EPM test was used to measure the anxiety levels in rats. Results of our present study showed that the time spent in open arm was significantly increased by drug (fluoxetine) as well as by fennel oil in rats suggested the anxiolytic effects of drug and fennel oil. However, the observed effects of antidepressant and anxiolytics were more prominent in fennel oil treated rats. These results are consistent with previously suggested effects of fennel oil from our lab (Perveen *et al*., 2014). Extensive studies carried out to understand the relationship of oxidative stress and psychiatric disorders pave the way to suggest the role of free radicals in the pathogenesis of depression and anxiety (Xu *et al*., 2014). The current studies suggest that the interrelationship between oxidative stress and psychiatric disorders may be due to oxidative stress-induced neuroinflammation, dysfunction of mitochondria, impaired neuroplasticity and deficits of signal transduction (Jindal *et al*., 2013; Aboul-Fotouh, 2013). The antioxidant effects of antidepressant and anxiolytics have demonstrated in various clinical and preclinical trials. The compelling evidence suggests that these drugs decrease oxidative stress by scavenging free radicals and inhibiting the oxidative pathway which may lead to the attenuation of depressive or anxiogenic symptoms (Dhingra *et al*., 2014; Zafir and Banu, 2007). The major constituents of essential oil of *F. vulgare* include anethole, fenchone, estragole and limonene. Anethole has shown anticarcinogenic and anti-inflammatory effects (Aggarwal *et al*., 2008). Other pharmacological activities of anethole include oestrogenic action, insecticide, anesthetic and antithrombotic activities (Chang and Ahn, 2002; Ponte *et al*., 2012). Studies have shown antioxidant property of anethole and its derivatives by inhibiting the lipid peroxidation. Anwar *et al*. (2009) investigated the antioxidant and antimicrobial activity of fennel oil and they found significant free radical scavenging and appreciable antioxidant activities.

To treat the depression, increased availability of serotonin (5-hydroxytryptamine; 5-HT) at the post-synaptic receptors is the main pharmacological target of antidepressants (Reddy *et al*., 1992). Inhibition of 5-HT reuptake or decreasing the activity of catabolic enzyme is involved in reducing the symptoms of depression. In a study conducted by Drukarch *et al*. (2006), anethole was reported to particularly inhibit the activity of monoamine oxidase B (MAO-B) enzyme. The increased catabolism of monoamines by MAO is involved in increased generation of free radicals leading to increase in oxidative stress

which may further worsen the psychiatric illnesses. Increased oxidative stress has been shown previously due to increased catabolism of 5-HT by MAO-B (Antkiewicz-Michaluk *et al*., 2014). Inhibition of MAO-B by anethole may also account for its antioxidative effects which may have the potential to alleviate the psychiatric disorders. Therefore, being the antioxidant and MAO-B inhibitor, anethole (main component of fennel oil) may be involved in decreasing the depressogenic and anxiogenic behaviors by increasing the availability of 5-HT towards its receptors in the synapse.

Although SSRIs are the most widely prescribed drug for the treatment of depression but these medications are reported to be associated with many side effects. Such side effects include weight gain, drugs interaction and sexual dysfunction. Increased serum cholesterol levels have been observed in patients using SSRIs for a longer period of time (Lee *et al*., 2016). Use of SSRIs upregulated the genes involve in the biosynthesis of cholesterol and fatty acids (Raeder *et al*., 2006). It has been reported that elevated cholesterol levels results in reduced response to fluoxetine treatment (Beyazyüz *et al*., 2013). In the present study, three weeks of fluoxetine administration induced increase in serum cholesterol level which was not observed in fennel oil treated rats. It is reported previously that fennel oil decreases cholesterol along with decrease in peroxidative damage (Choi and Hwang, 2004), suppresses blood lipid level (Shahat *et al*., 2011) inhibits fat absorption (Han *et al*., 2002) and enhances beta oxidation (Kulisic-Bilusic *et al*., 2010). Thus, it can be suggested that the potential antidepressant and anxiolytic effects of fennel oil observed in this study may be attributed to its antioxidant property (Roby *et al*., 2013).

CONCLUSION

In the present study, at the first time, we suggest that depressive- and anxiogenic-behaviors can be reversed by the repeated administration of fennel oil which showed efficacy comparable to that of the clinically used synthetic drug, fluoxetine. Moreover, repeated administration of fennel oil is not associated with the metabolic disturbance as evident by normal serum cholesterol levels. Further investigations are needed to explore these anti-psychiatric effects and the possible underlying biochemical mechanism in animal model of depression and anxiety before recommending the use of fennel oil for the treatment of psychiatric disorders.

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Statement of conflict of interest

Authors declare no conflict of interest

REFERENCES

Aboul-Fotouh, S., 2013. Coenzyme Q10 displays antidepressant-like activity with reduction of hippocampal oxidative/nitrosative DNA damage in chronically stressed rats. *Pharmacol. Biochem. Behav.,* **104**: 105-112. https://doi.org/10.1016/j.pbb.2012.12.027

Aggarwal, B.B., Kunnumakkara, A.B., Harikumar, K.B., Tharakan, S.T., Sung, B. and Anand, P., 2008. Potential of spice-derived phytochemicals for cancer prevention. *Planta Med.,* **74**: 1560. https://doi.org/10.1055/s-2008-1074578

Antkiewicz-Michaluk, L., Wąsik, A., Możdżeń, E., Romańska, I. and Michaluk, J., 2014. Antidepressant-like effect of tetrahydroisoquinoline amines in the animal model of depressive disorder induced by repeated administration of a low dose of reserpine: behavioral and neurochemical studies in the rat. *Neurotox. Res.,* **26**: 85-98. https://doi.org/10.1007/s12640-013-9454-8

Anwar, F., Ali, M., Hussain, A.I. and Shahid, M., 2009. Antioxidant and antimicrobial activities of essential oil and extracts of fennel (*Foeniculum vulgare* Mill.) seeds from Pakistan. *Flavour Fragr. J.,* **24**: 170-176. https://doi.org/10.1002/ffj.1929

Aswar, U., Chepurwar, S., Shintre, S. and Aswar, M., 2017. Telmisartan attenuates diabetes induced depression in rats. *Pharmacol. Rep.,* **69**: 358-364. https://doi.org/10.1016/j.pharep.2016.12.004

Badgujar, S.B., Patel, V.V. and Bandivdekar, A.H., 2014. *Foeniculum vulgare* Mill: A review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. *BioMed. Res. Int.,* **2014**: 842674. https://doi.org/10.1155/2014/842674

Barros, L., Carvalho, A.M. and Ferreira, I.C., 2010. The nutritional composition of fennel (*Foeniculum vulgare*): shoots, leaves, stems and inflorescences. *LWT Fd. Sci. Technol.,* **43**: 814-818. https://doi.org/10.1016/j.lwt.2010.01.010

Berk, M., Kapczinski, F., Andreazza, A., Dean, O., Giorlando, F., Maes, M., Yücel, M., Gama, C., Dodd, S. and Dean, B., 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci. Biobehav. Rev.,* **35**: 804-817.

https://doi.org/10.1016/j.neubiorev.2010.10.001

Beyazyüz, M., Albayrak, Y., Eğilmez, O.B., Albayrak, N. and Beyazyüz, E., 2013. Relationship between ssris and metabolic syndrome abnormalities in patients with generalized anxiety disorder: A prospective study. *Psychiat. Investig.,* **10**: 148-154. https://doi.org/10.4306/pi.2013.10.2.148

Bilia, A.R., Fumarola, M., Gallori, S. and Mazzi, G., 2000. Vincieri F. Identification by HPLC-DAD and HPLC-MS analyses and quantification of constituents of fennel teas and decoctions. *J. Agric. Fd. Chem.,* **48**: 4734-4738. https://doi.org/10.1021/jf000171n

Chang, K.S. and Ahn, Y.J., 2002. Fumigant activity of (E)-anethole identified in Illicium verum fruit against Blattella germanica. *Pest Manage. Sci.,* **58**: 161-166. https://doi.org/10.1002/ps.435

Choi, E.M. and Hwang, J.K., 2004. Antiinflamatory, analgesic and antioxidant activities of the fruit of *Foeniculum vulgare*. *Fitoterapia*, **75**: 557-565. https://doi.org/10.1016/j.fitote.2004.05.005

Dhingra, M.S., Dhingra, S., Kumria, R., Chadha, R., Singh, T., Kumar, A. and Karan, M., 2014. Effect of trimethylgallic acid esters against chronic stress-induced anxiety-like behavior and oxidative stress in mice. *Pharmacol. Rep.,* **66**: 606-612. https://doi.org/10.1016/j.pharep.2014.01.004

Drukarch, B., Flier, J., Jongenelen, C., Andringa, G. and Schoffelmeer, A., 2006. The antioxidant anethole dithiolethione inhibits monoamine oxidase-B but not monoamine oxidase A activity in extracts of cultured astrocytes. *J. Neural. Transm.,* **113**: 593-598. https://doi.org/10.1007/s00702-005-0350-0

Dua, A., Garg, G. and Mahajan R., 2013. Polyphenols, flavonoids and antimicrobial properties of methanolic extract of fennel (*Foeniculum vulgare* Miller). *Eur. J. exp. Biol.,* **3**: 203-208.

El-Soud, N., El-Laithy, N., El-Saeed, G., Wahby, M., Khalil, M., Morsy, F. and Shaffie, N., 2011. Antidiabetic activities of *Foeniculum vulgare* mill. Essential oil in streptozotocin-induced diabetic rats. *Maced. J. med. Sci.,* **4**: 139-146.

Everitt, A.V., Hilmer, S.N., Brand-Miller, J.C., Jamieson, H.A., Truswell, A.S., Sharma, A.P., Mason, R.S., Morris, B.J. and Le, Couteur, D.G., 2006. Dietary approaches that delay age-related diseases. *Clin. Interv. Aging,* **1**: 11-31. https://doi.org/10.2147/ciia.2006.1.1.11

García-Jiménez, N., Péerez-Alonso, M.J. and Velasco-Negueruela, A., 2000. Chemical composition of fennel oil, *Foeniculum vulgare* Miller, from Spain. *J. Essent. Oil Res.,* **12**: 159-162.

Haider, S., Liaquat, L., Shahzad, S., Sadir, S., Madiha, S., Batool, Z., Tabassum, S., Saleem, S., Naqvi, F. and Perveen, T., 2015. A high dose of short term exogenous D-galactose administration in young male rats produces symptoms simulating the natural aging process. *Life Sci.,* **124**: 110-119. https://doi.org/10.1016/j.lfs.2015.01.016

Han, L.K., Zheng, Y.N., Xu, B.J., Okuda, H. and Kimura, Y., 2002. Saponins from platycodi radix ameliorate high fat diet-induced obesity in mice. *J. Nutr.,* **132**: 2241-2245.

Jindal, A., Mahesh, R. and Bhatt, S., 2013. Etazolate, a phosphodiesterase 4 inhibitor reverses chronic unpredictable mild stress-induced depression-like behavior and brain oxidative damage. *Pharmacol. Biochem. Behav.,* **105**: 63-70. https://doi.org/10.1016/j.pbb.2013.01.020

Karabulut-Bulan, O., Bolkent, S., Kizir, A. and Yanardag, R., 2016. Protective effects of vitamin e and selenium administration on small intestinal damage prior to abdominal radiation. *Pakistan J. Zool*., **48**: 1225-1232.

Kessler, R., Adler, L., Berglund, P,. Green, J.G., McLaughlin, K., Fayyad, J., Russo, L., Sampson, N., Shahly, V. and Zaslavsky, A., 2014. The effects of temporally secondary co-morbid mental disorders on the associations of DSM-IV ADHD with adverse outcomes in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *Psychol. Med.,* **44**: 1779-1792. https://doi.org/10.1017/S0033291713002419

Kulisic-Bilusic, T., Blažević, I., Dejanović, B., Miloš, M. and Pifat, G., 2010. Evaluation of the antioxidant activity of essential oils from caper (*Capparis spinosa*) and sea fennel (*Crithmum maritimum*) by different methods. *J. Fd. Biochem.,* **34**: 286-302. https://doi.org/10.1111/j.1745-4514.2009.00330.x

Lee, K.G. and Shibamoto, T., 2001. Antioxidant activities of volatile components isolated from Eucalyptus species. *J. Sci. Fd. Agric.,* **81**: 1573-1579. https://doi.org/10.1002/jsfa.980

Lee, K.G., Mitchell, A.E. and Shibamoto, T., 2000. Determination of antioxidant properties of aroma extracts from various beans. *J. Agric. Fd. Chem.,* **48:** 4817-4820. https://doi.org/10.1021/jf000442u

Lee, S.H., Paz-Filho, G., Mastronardi, C., Licinio, J. and Wong, M.L., 2016. Is increased antidepressant exposure a contributory factor to the obesity pandemic? *Transl. Psychiat.,* **6**: e759. https://doi.org/10.1038/tp.2016.25

Lee, S.Y., Lee, S.J., Han, C., Patkar, A.A., Masand, P.S. and Pae, C.U., 2013. Oxidative/nitrosative

stress and antidepressants: targets for novel antidepressants. *Prog. Neuropsychopharmacol. Biol. Psychiat.,* **46**: 224-235. https://doi.org/10.1016/j.pnpbp.2012.09.008

Mansour, S.A., Heikal, T.M., Refaie, A.A. and Mossa, A., 2011. Antihepatotoxic activity of fennel (*Foeniculum vulgare* Mill.) essential oil against chlorpyrifos-induced liver injury in rats. *Global J. environ. Sci. Technol.,* **1**: 1-10.

Nagórna-Stasiak, B., 1987. Effect of cholesterol on intestinal motility in rabbits in chronic experiments. *Pol. Arch. Weter.,* **24**: 445-455.

Naqvi, F., Haider, S., Perveen, T. and Haleem, D.J., 2012. Sub-chronic exposure to noise affects locomotor activity and produces anxiogenic and depressive like behavior in rats. *Pharmacol. Rep.,* **64**: 64-69. https://doi.org/10.1016/S1734-1140(12)70731-4

Oktay, M., Gülçin, İ. and Küfrevioğlu, Ö.İ., 2003. Determination of *in vitro* antioxidant activity of fennel (*Foeniculum vulgare*) seed extracts. *L.W.T. Fd. Sci. Technol.,* **36**: 263-271. https://doi.org/10.1016/S0023-6438(02)00226-8

Özbek, H., Uğraş, S., Dülger, H., Bayram, I., Tuncer, I., Öztürk, G. and Öztürk, A., 2003. Hepatoprotective effect of *Foeniculum vulgare* essential oil. *Fitoterapia,* **74**: 317-319. https://doi.org/10.1016/S0367-326X(03)00028-5

Perveen, T., Yousuf, S., Razi, F., Zuberi, N.A., Tabassum, S. and Haider, S., 2014. Involvement of altered serotonergic responses in fennel oil induced antidepressant, anxiolytic and antinociceptive effects in rats. *World J. Pharm. Sci.,* **2**: 493-498.

Ponte, E.L., Sousa, P.L., Rocha, M.V., Soares, P.M., Coelho-de-Souza, A.N., Leal-Cardoso, J.H. and Assreuy, A.M., 2012. Comparative study of the anti-edematogenic effects of anethole and estragole. *Pharmacol. Rep.,* **64**: 984-990. https://doi.org/10.1016/S1734-1140(12)70895-2

Porsolt, R., Bertin, A. and Jalfre, M., 1977. Behavioral despair in mice: a primary screening test for antidepressants. *Arch. Int. Pharmacodyn. Ther.,* **229**: 327-336.

Pradhan, M., Sribhuwaneswari, S., Karthikeyan, D., Minz, S., Sure, P., Chandu, A.N., Mishra, U., Kamalakannan, K., Saravanankumar, A. and Sivakumar, T., 2008. *In vitro* cytoprotection activity of *Foeniculum vulgare* and *Helicteres isora* in cultured human blood lymphocytes and antitumour activity against B16F10 melanoma cell line. *Res. J. Pharm. Technol.,* **1**: 450-452.

Raeder, M.B., Bjelland, I., Emil, Vollset, S. and Steen, V.M., 2006. Obesity, dyslipidemia and diabetes with selective serotonin reuptake inhibitors: The Hordaland health study. *J. clin. Psychiatry,* **67**: 1974-1982. https://doi.org/10.4088/JCP.v67n1219

Rather, M.A., Dar, B.A., Sofi, S.N., Bhat, B.A. and Qurishi, M.A., 2016. *Foeniculum vulgare*: A comprehensive review of its traditional use, phytochemistry, pharmacology and safety. *Arabian J. Chem.,* **9**: S1574-S1583. https://doi.org/10.1016/j.arabjc.2012.04.011

Reddy, P.L., Khanna, S., Subhash, M., Channabasavanna, S. and Rao, B.S.R., 1992. CSF amine metabolites in depression. *Biol. Psychiat.,* **31**: 112-118. https://doi.org/10.1016/0006-3223(92)90198-9

Roby, M.H.H., Sarhan, M.A., Selim, KA-H. and Khalel, K.I., 2013. Antioxidant and antimicrobial activities of essential oil and extracts of fennel (*Foeniculum vulgare* L.) and chamomile (*Matricaria chamomilla* L.). *Ind. Crop Prod.,* **44**: 437-445. https://doi.org/10.1016/j.indcrop.2012.10.012

Senatore, F., Oliviero, F., Scandolera, E., Taglialatela-Scafati, O., Roscigno, G., Zaccardelli, M. and de Falco, E., 2013. Chemical composition, antimicrobial and antioxidant activities of anethole-rich oil from leaves of selected varieties of fennel [*Foeniculum vulgare* Mill. ssp. *vulgare* var. *azoricum* (Mill.) Thell]. *Fitoterapia,* **90**: 214-219. https://doi.org/10.1016/j.fitote.2013.07.021

Shahat, A.A., Ibrahim, A.Y., Hendawy, S.F., Omer, E.A., Hammouda, F.M., Abdel-Rahman, F.H. and Saleh, M.A., 2011. Chemical composition, antimicrobial and antioxidant activities of essential oils from organically cultivated fennel cultivars. *Molecules,* **16**: 1366-1377. https://doi.org/10.3390/molecules16021366

Xu, Y., Wang, C., Klabnik, J.J. and O'Donnell, J.M., 2014. Novel therapeutic targets in depression and anxiety: Antioxidants as a candidate treatment. *Curr. Neuropharmacol.,* **12**: 108-119. https://doi.org/10.2174/1570159X11666131120231448

Zafir, A. and Banu, N., 2007. Antioxidant potential of fluoxetine in comparison to *Curcuma longa* in restraint-stressed rats. *Eur. J. Pharmacol.,* **572**: 23-31. https://doi.org/10.1016/j.ejphar.2007.05.062