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872 *Current Drug Targets,* **2013**, *14*, 872-879

Aromatherapy and the Central Nerve System (CNS): Therapeutic Mechanism and its Associated Genes

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Abstract: Molecular medical research on aromatherapy has been steadily increasing for use as an adjuvant therapy in managing psychiatric disorders and to examine its therapeutic mechanisms. Most studies, as well as clinically applied experience, have indicated that various essential oils, such as lavender, lemon and bergamot can help to relieve stress, anxiety, depression and other mood disorders. Most notably, inhalation of essential oils can communicate signals to the olfactory system and stimulate the brain to exert neurotransmitters (e.g. serotonin and dopamine) thereby further regulating mood. However, little research has been done on the molecular mechanisms underlying these effects, thus their mechanism of action remains ambiguous. Several hypotheses have been proposed regarding the therapeutic mechanism of depression. These have mainly centered on possible deficiencies in monoamines, neurotrophins, the neuroendocrine system, c-AMP, cation channels as well as neuroimmune interactions and epigenetics, however the precise mechanism or mechanisms related to depression have yet to be elucidated. In the current study, the effectiveness of aromatherapy for alleviating psychiatric disorders was examined using data collected from previously published studies and our unpublished data. A possible signaling pathway from olfactory system to the central nerve system and the associated key molecular elements of aromatherapy are also proposed.

Keywords: Aromatherapy, central nerve system, essential oils, psychiatric disorders.

INTRODUCTION

Nature is unquestionably the finest resource for discovering diverse medicines. Medicinal plants contain secondary metabolites with health promoting effects that often have therapeutic potential. Therefore, it is no surprise that aromatic plants may also have medicinal benefits in humans. The application of aromatic compounds derived from these plants has a long history. They were used by the Chinese in the form of incense, by the Egyptians for embalming the dead and by the Romans in baths and beauty. The term, aromatherapy, was created by the French chemist, Gattefossé who tried using lavender oil for wound healing. Later, as aromatherapy developed and with the emerging field of psychoneuroimmunology, it began to be used to alleviate emotional and mental pain.

Mixtures of volatile aromatic compounds (mainly mono- and ses-quiterpenoids, benzoids and phenylpropanoids, etc.), called essential oils, are isolated from the "essence" of plants or herbs. Essential oils can have different biological actions in humans, animals and other plants [1]. They can be made as perfumes, cosmetics or soaps in the "beauty industry", as flavors for foods and drinks and can be used in the medical industry. Aromatic compounds in essential oils can have antiseptic, antimicrobial and antiviral effects and often demonstrate great cytotoxicity in cancer cells [2]. Aromatherapy is a branch of alternative medicine that uses essential oils for therapeutic purposes *via* direct inhalation, bath or massage. Some essential oils have direct pharmacological effects, though more often, essential oils affect the limbic system of the brain *via* the olfactory system. The effectiveness of aromatherapy for the management of anxiety, depression and other mental disorders is described in the current study. Empirical evidence of aromatic usage in ancient times and present aromatic research indicates that aromatherapy is definitely one of the fastest growing areas in complementary and alternative medicine (CAM). The current study examines the research on the molecular aspects of aromatherapy and proposes tentative signal pathways for the effect of aromatherapy on the central nerve system (CNS) through stimulation of the olfactory system.

USE OF AROMATHERAPY FOR ALLEVIATION OF PSYCHIATRIC DISORDERS: RESEARCH ON THE CNS

These days, many people suffer from anxiety, restlessness, insomnia, depression and other mood disorders that are mainly caused by recurrent pressures, threats and stresses due to work, illness and life in general. It has been reported that 39–47% of peri-menopausal women and 35–60% of post-menopausal women have problems with sleeping [3]. Psychiatric disorders such as anxiety and stress are likely related to the mechanisms that underlie poor sleep quality. It has been estimated that 85 to 90% of individuals who die

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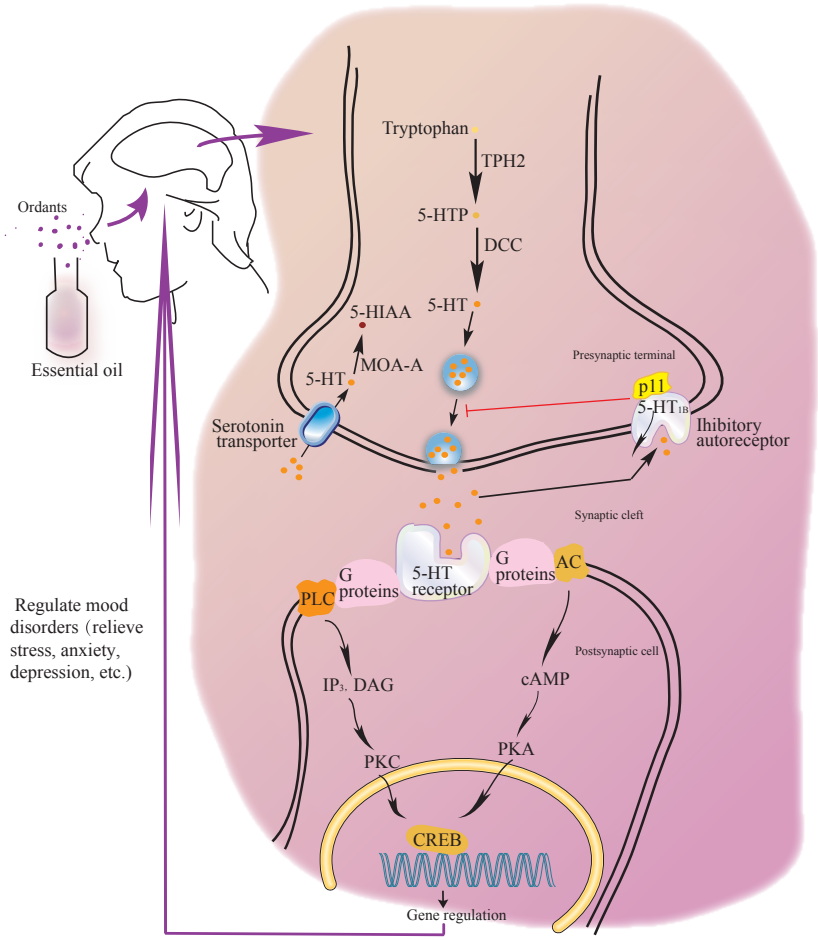

Fig. (1). The effects of essential oils on 5-HT pathway *via* olfaction. The molecules of inhaled essential oils transmit their signals *via* olfaction and stimulate the brain to produce 5-HT. The 5-HT-induced pathway is important in mood regulation (depression, anxiety, etc.). 5-HT is synthesized from tryptophan, which is catalyzed by tryptophan hydroxylase. It is restored in the vesicles in the presynaptic neuron and, once stimulated by nerve impulse, it will be released into the synaptic cleft. Then 5-HT acts on its receptor to activate G-protein-coupled-pathways and finally phosphorylates the transcription factor, cyclic-AMP-response-element-binding protein (CREB) to regulate related-gene expression. This contributes to the neurotransmitter alteration, nerve excitability, neurogenesis and neuroplasticity, cell death and atrophy observed in mood disorders. Stimulation by essential oils can inhibit the actions of the neurotransmitters such as the reuptake of serotonin *via* serotonin transporters and the feedback control of the release *via* 5-HT_{1B} regulatory autoreceptors in the presynaptic neuron. Protein p11 interacts with 5-HT_{1B} receptors, which can enhance their function.

from suicide had been diagnosed with a psychiatric disorder, mainly severe depression. However, existing treatments for many psychiatric disorders are unsatisfactory and also carry the risk of side effects such as suicide or adverse drug responses (ADR). Fortunately, a great number of prominent aromatherapy studies have shown promising results for the alleviation of depression, anxiety and other stress-related illnesses. Aromatherapy has been applied extensively, all over the world, for the therapeutic management of mental disorders [4, 5]. For example, in Australia people who were experiencing mild to moderate depression routinely accepted aromatherapy treatment given by complementary and alternative medical practitioners [6]. Thus far, aromatherapy studies have primarily explored individuals' physiological, psychological and spiritual responses to inhaled, ingested or topically applied essential oils.. A review of the clinical benefits of aromatherapy found that aromatherapy was pleasant, slightly anxiolytic and often enjoyable for patients in stressful situations [7]. Accumulating evidence suggests that essential oils that are inhaled or dermally applied exert measureable psychological effects. Perry *et al.* reported that essential oils derived from bergamot, jasmine, lavender, rose and geranium had antidepressant effects [8]. Antidepressant effects, resulting from olfactory stimulation by various odorants, were observed in the rodent model during the forced swimming test. Results showed that lemon odor significantly reduced total immobility time; a similar result to that observed with clinical antidepressants. Another study found that citral, one of the main components of lemon odor, was as effective in the forced swimming test as was lemon odor, even when used alone [9]. Lemon K, reported that 32 acute care, psychiatric patients who received essential oils and inhaled aromatic odors during aroma-therapeutic massage, showed significant improvement in scores of depression,

anxiety and severity of emotional symptoms compared to controls [10]. Popular anxiolytic essential oils from plants are multifarious, and include lavender, rose, orange, bergamot, lemon, sandalwood, clary sage, roman chamomile and rose-scented geranium [11]. Lavender oil is the most studied phytotherapeutic for use as an anxiolytic. Two studies on the use of lavender oil aromatherapy, one in surgical patients [12] and the other in patients undergoing gastroscopy [13], showed that the groups receiving lavender oil had markedly lower anxiety than the control (non-lavender) groups. Use of lavender oil was also investigated in another study on dental patients [14]. Additionally, lavender oil may provide mild sedation and promote sleep. In one study in Taiwan, middle-aged women with insomnia reported significantly improved quality of sleep after 12 weeks of aromatherapy treatment in which they inhaled lavender oil [15]. These studies indicate that aromatherapy may be an effective, alternative treatment in clinical settings.

Mechanistic and neuropharmacological studies of the effects of essential oils and/or their chemical constituents have also been shown both *in vitro* and *in vivo*. Linalool, a major component of lavender, has been found to inhibit glutamate binding, and might function as tranquilizer [16]. Pinene, a prime component of lemon and lavender, was reported to potentiate sedative responses in the presence of gamma-aminobutyric acid (GABA), at low concentrations, but to inhibit sedative responses in the presence of high GABA concentrations *in vitro* [4]. Carvacrol (5-isopropyl-2-methylphenol) has a characteristic pungent, warm taste and odor and is a major component of the thyme essential oil. Its anxiolytic effects have been studied in several rat models using tests such as the elevated, plus-maze task (EPM) and the open-field test. Carvacrol may also be involved with GABAergic transmission [17]. Similarly, black cumin oil, taken orally, is a useful choice for the treatment of anxiety. It has been shown to improve cerebral levels of serotonin while reducing serotonin's main metabolite, 5-hydroxyindole acetic acid (5-HIAA). Tryptophan levels in the brain and plasma were found to have increased as well [18]. Research assessing the effects of citrus essential oils on physical and/or psychological stress found that, the principal components of these oils, including gamma-terpinene, citral and (S)–limonene in particular, dramatically inhibited monoamine-induced elevation of psychological stress [19]. In one study, mice treated with lavender oil had increased expression of the dopamine D3 receptor subtype in the olfactory bulb. This could be a factor in lavender oil-induced behavioral changes [20].

USE OF AROMATHERAPY FOR TREATMENT OF PSYCHIATRIC DISORDERS: MOLECULAR MECHANISMS

Depression and Serotonin-Transporter–Linked Polymorphic Region (5-HTTLPR)

Stressful life events, such as examinations, work, divorce or financial problems have a substantial, causal association with many mental disorders including depression and anxiety [21]. The European Brain Council (EBC) has estimated that the annual cost of depression is around one-hundred billion EUR and affects approximately 21 million people across 28 European countries [22]. Depression is a heterogeneous, psychiatric disease, the diagnosis of which relies on a wide spectrum of symptoms including low mood, inability to experience pleasure, irritability, difficulty in thinking or concentration and abnormalities in appetite and sleep, that result in significant dysfunction(s) in daily life [23]. Many symptoms of depression are similar to those of anxiety. In fact, depression and anxiety frequently overlap and are co-occurrent [24]. However, it is often difficult to differentiate between the two when making a diagnosis based on behavioral and mental symptoms. This undoubtedly presents analytical barriers to understanding depression through genomic studies, autopsy investigations and neuroimaging. Suicide is a common outcome in patients with severe depression. Moreover, depression should not be considered as a single disease. It often accompanies pain resulting from cancer, diabetes and/or other chronic diseases. In fact, depression may become the second major cause of death and disability after cardiovascular diseases, worldwide, by 2020 [25]. The treatment of depression has been a tactical concern among clinicians, patients and researchers.

Depression is a favorably, heritable disorder with a genetic risk of 40%-50% [26]; the risk is considerably higher for early-onset, severe and recurrent depression. Yet, the genes involved in depression and the associated mechanism(s) have not been identified clearly. The serotonin-transporter–linked polymorphic region (5-HTTLPR) is a degenerate, repeat, polymorphic region in SLC6A4 (encoding for the serotonin- transporter), and is linked to neuropsychiatric disorders including depression, anxiety and pessimism [27]. Polymorphism of 5-HTTLPR diminishes the uptake of the neurotransmitter, serotonin, into the presynaptic cells in the brain, but the correlation between depression and 5-HTTLPR/serotonin is still vague [28]. In addition to genetic component(s), non-genetic factors, including stress, emotional pain, microbial infection (e.g., Borna virus, flu or *H. pylori*), side effects of drugs (e.g., isotretinoin, selective serotonin reuptake inhibitors (SSRIs) or α-interferon) or malignant tumors (e.g., non-small cell lung cancer, head-neck cancer or prostate cancer) can also trigger the occurrence or recurrence of depression [25, 29].

Depression and Monoamines

Theories for the pathophysiology of depression that have been proposed include the monoamine-deficiency hypothesis, the neurotrophin hypothesis the neuroendocrine and neuroimmune interaction hypothesis and the epigenetic hypothesis [25, 29]. Based on several clinical observations of antidepressants, the monoamine-deficiency hypothesis (mainly a shortage of noradrenaline and serotonin) has been recognized as the mainstream model throughout the central nervous system (CNS). Animal models used to study depression (the Flinders sensitive line (FSL) rat, the learned helpless (LH) rat, …etc.) and behavior tests (the forced swim test, chronic mild stress, …etc.) have shown that virtually every compound that inhibits norepinephrine and/or serotonin reuptake, behaves as a clinically successful antidepressant and has great potential for development as antidepressant drugs [30]. Moreover, gene knockout studies also strongly support the monoamine hypothesis of depression development. For ex-

ample, the serotonin-reuptake–transporter knockout mouse is excessively anxious and was characterized by immobility during the forced swim test [31]. The mechanisms of action of the other leading classes antidepressant drugs, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) further support the monoamine hypothesis. These drugs have evolved to a great extent since they were first used in the 1960's. MAOIs, such as iproniazid, irreversibly inhibit the key metabolic enzymes of monoamines, resulting in a comprehensive increase of monoamine levels in the brain [32]. TCAs, such as imipramine, are named after their chemical structure and are derived from phenothiazines. TCAs block monoamine membrane transporters, leading to increased extracellular availability of monoamine neurotransmitters [33]. The antihypertensive drug, reserpine, depletes storage vesicles that contain noradrenaline and other monoamines, and produces pro-depressive effects, thus providing even more evidence of the anti-depressant effect of monoamines [25, 29, 32]. Additionally, mechanisms of action of 2nd-generation antidepressants add further credence to the monoamine hypothesis. These drugs are designed to strongly increase monoamines levels through inhibition of monoamine reuptake by presynaptic neurons or by acting as antagonists for selected monoamine receptors (for example, SSRIs such as fluoxetine) [34]. The effective use of these drugs has supplied critical evidence supporting the monoamine hypothesis of depression and has provided a good template for the development of new anti-depressant drugs [35].

Aroma-Therapeutic Effects in the CNS of Depression Patients

The serotonergic and noradrenergic systems exist throughout the entire brain and modulate many aspects of feeling, thinking and behavior. According to the monoamine hypothesis of depression treatment, monoamines reduce the uptake and availability of serotonin and noradrenaline.

Teruhisa Komoria *et al.* demonstrated that lemon odor had antidepressant effects in rats that had undergone the forced swimming test, however the exact mechanism for the antidepressant effect of lemon odor was not examined [9]. In another study, it was reported that lemon oil vapor significantly accelerated the turnover rate of 5-hydroxytryptamine (5-HT) metabolism in the prefrontal cortex and striatum of a rodent model, implying that 5-HT molecules, 5-HT1A receptors and their associated pathways might be involved in the antidepressant mechanism of essential oil odorants [36]. The above studies indicate that the mechanism for the antidepressant effects of essential oils (i.e. regulating 5-HT levels) is similar to that of the best antidepressants currently available in the therapeutic drug pool.

Serotonin Hypothesis of Depression

The fact that the common treatments for the symptoms of anxiety and depression are the same indicates that they may share the same or a similar neurobiological dysfunction. 5-HT (also known as serotonin) is a monoamine neurotransmitter, primarily found in the alimentary canal, that regulates intestinal movements [34]. In the central nervous system (CNS), serotonin modulates mood and behavior and contributes to feelings of well-being and happiness. Because of this, it is thought of, and often called, a "happy chemical" in the brain.

The synthesis of serotonin in the brain occurs in a small network of metabolic pathways. L-tryptophan, the precursor of 5-HT, crosses into the brain through the blood brain barrier and is converted to 5-hydroxytryptophan (5-HTP) by the brain-specific tryptophan hydroxylase 2(TPH2) [37]. 5-HTP is then promptly catalyzed by the amino acid decarboxylase (DDC) to 5-HT. Studies show that tryptophan depletion triggers a transient return of depressive symptoms in patients who have been successfully treated with serotonin-reuptake inhibitors [38]. Enhancing the levels of 5-HT seems to be important for the treatment of depression. This also provides evidence for the role of abnormal serotonergic function in depression.

In the presynaptic neuron, 5-HT is synthesized and stored in vesicles. It is released into the synaptic cleft *via* exocytosis, thereby influencing both presynaptic and postsynaptic neurons. The 5-HTT gene (slc6a4), encodes the serotonin transporter and is responsible for the reuptake of serotonin into the presynaptic cell after it has been released into the synaptic cleft to signal the postsynaptic neuron. Hence it has become a popular target for antidepressant drugs such as SSRIs. Genes involved in the central network like 5-HTT have been intensively investigated in order to discover genetic risk factors for depression. Due to the polymorphism of its promoter, levels of 5-HTT vary in the human population. Of particular interest is the short allele of 5-HTT which seems to carry a higher risk for the development of depression in individuals, especially when accompanied by stressful life events [28].

Reuptake of 5-HT into the presynaptic cell is degraded into 5-HIAA by monoamine oxidase (MOA). Recently, results from a positron-emission tomographic (PET) study indicated an over 30% increase of the enzyme in patients with depression after application of a reporting ligand for brain MOA [39]. Therefore, the discovery and development of antidepressants targeted at inhibiting monoamine oxidase and reducing 5-HIAA levels, are believed to reveal reduced neuronal activities [36].

The inhibition of 5-HT reuptake, transportation or its related metabolism causes an increase in extracellular 5-HT that is immediately sensed by the autoreceptors, 5-HT_{1A} and 5-HT_{1B}. This leads to the inhibition of the "discharge" of neurons and of 5-HT levels as well [40]. Therefore, 5-HT_{1A} antagonists (buspiron, gepiron) were developed for the treatment of depression and anxiety. The 5-HT_{1B} receptors reside in pre-synaptic cells and interact with the calcium-binding protein, p11, to regulate the release of serotonin through feedback inhibition. Studies show that the levels of p11 are higher in individuals who have been on chronic SSRI treatment and lower in the brains of post-mortem depressed individuals [41].

Identifying the 5-HT receptor subtypes, and the possible malfunctions in the signaling pathway that are involved in depression, is another important component for the development of antidepressant drugs. The 5-HT_3 receptor is a

ligand-gated Na^+ and K^+ cation channel that activates an intracellular second messenger cascade that conducts a similar pathway and response. No matter which of the 5-HTT subtypes positively coordinate with adenylate cyclase (5-HT_4, 5-HT_6, 5-HT_7) or phospholipase C (PLC) to stimulate Ca^{2+}-dependent kinases (5-HT_{2A}, 5-HT_{2C}), they are all thought to up- regulate the transcription factor, cyclic-AMP-response-element- binding proteins (CREB) and MAP kinase-dependent kinases (MAPK). These are believed to be the effective criteria for the discovery and development of antidepressant drugs [42, 43]. The concentrations of inositol and cyclic AMP in the brain of depressed patients were much lower than in normal, non-depressed people when CREB and MAPK were activated. Once CREB levels in the rodent brain were increased through 5-HT serotonin treatment, the antidepressant effects were significant [44-46]. CREB is activated by phosphorylation at serine 133 (Ser133). As a transcription factor, it serves as a convergence point for multiple pathways of neurotransmitters [47]. Once activated, CREB regulates the expression of serotonin pathway-related genes and enhances the action of 5-HT, ion-channel related genes. This influences nerve excitability, neurogenesis and neuroplasticity related genes, such as brain-derived neurotrophic factor (BDNF), to stimulate regeneration of neurons in depression. Generally speaking, CREB is an important target for many psychiatric drugs.

Limitations of the Effectiveness of Monoamine Antidepressants

Monoamine-based antidepressants offer better therapeutic efficacy and have been a mainstay for the treatment of depression thus far. Unfortunately, nearly one third of depressed patients suffer unpleasant side effects such as hypertension, headaches, insomnia and nausea [48] and up to 50% of patients fail to have an adequate therapeutic response even after a treatment switch [49]. Moreover, P-glycoprotein, which is responsible for transporting small molecules back into the blood circulation across the blood-brain barrier (BBB), also obstructs the efficacy and effect of monoamine-based antidepressants, including some SSRIs [32]. The polymorphisms of the gene coding for P-glycoprotein also remarkably influence the effects of these antidepressants, thus limiting wide use of these drugs. Psychological treatment for depression, such as cognitive behavioral therapy, is also popular. However, positive results from such treatments have not been convincing. Due to the limitations of conventional treatment, it is essential that adjuvant treatment or alterative medicine, such as aromatherapy, be seriously evaluated for the treatment of depression.

AROMA-SENSING IN THE OLFACTORY SYSTEM

As shown above, the underlying mechanisms for the alleviation of psychiatric disorders by essential oils may be similar to those of anti- psychotic drugs. In contrast with current oral drugs used for the treatment of psychiatric disorders, essential oils produce pharmacologic effects, not only by the absorption through the skin and upper respiratory tract (URT), but also *via* the sense of smell.

The sense of smell is a vital pathway to communicate with the environment in both humans and animals. It is correlated with daily functions such as alertness, relaxation and joyfulness which might be significantly mediated by different aromas or scents [50]. Several studies have found that different odors can powerfully adjust mood and atmosphere. For example, people in the presence of a pleasant odor tend to retain a positive mood and are more likely to employ efficient work strategies [51]. Conversely, an unpleasant odor reduced people's subjective judgments and lowered their tolerance for frustration [52]. Peppermint and rosemary are thought to increase arousal and excitement, to improve cognition and memory and to enhance performance on cognitive assessments [53]. The prevalence of "Forest Hospital" and "Floral Hospital" in Europe take advantage of natural aromas and peaceful environments to regulate the patients' physical and mental states. It has been found that patients in the early stages of Alzheimer's disease or Parkinson disease might lose the sense of smell, therefore, research on the olfactory system may provide new options for the prevention, detection, and/or treatment of these diseases [54].

The olfactory system is a complex network, comprised mainly of the olfactory epithelium, the olfactory bulb and the olfactory cortex. Inhaled air carries volatile odorant molecules to the olfactory epithelium, which is located in the roof of the two nasal cavities of the human nose. Olfactory epithelium contains approximately 50 million primary, sensory receptor cells that serve a chemosensory function as well as other cell types that have assistant functions, such as providing support for the regeneration of receptor cells [55]. The mucous layer, produced by the Bowman's glands in the olfactory epithelium, forms a sol phase of low viscosity that envelops the cilia of sensory receptor cells and assists in transporting and concentrating odorants. The odorant molecules interact with the olfactory receptors (ORs) located in the cilia. The ORs are involved in G protein–coupled activation in the olfactory epithelium and produce the signal cascade that our brain translates as odor. Linda Buck and Richard Axel found that there are roughly one thousand odorant receptor genes in humans and that each olfactory neuron expresses only one type of olfactory receptor on its membrane surface [56]. Known specific odorants for OR genes have been reported. For example, helional has a sweet hay-like odor and is recognized by human OR17-40 (located at chromosome 17pl3.3) [57]. In addition, the mouse OR genes for limonene, an aromatic hydrocarbon of lemon and carvone that has a spearmint odor, are each found at a different chromosomal locus (chromosomes 5q35.3, and 9q34.11, respectively) [58]. Different combinations of receptors recognize different odorants, much like the 26 letters of the alphabet combine to create numerous words. The olfactory system uses a combinatorial coding system to discriminate among or encode various odors. This enables 1,000 receptors to describe and distinguish many thousands of odors [59]. Trivial differences in chemical structure and concentration both induce distinctive responses. For example, (+) linalool is perceived as a sweet, floral odor, but (−) linalool is perceived to have a woody, lavender quality [60].

Gene knockout studies have indicated that olfactory receptors trigger a cAMP cascade in olfactory neurons in response to stimulus by odorants. This cascade contains three

components: stimulatory G-protein α subunits (Gαolf), adenylyl cyclase type III and cyclic nucleotide-gated channels [61]. Another olfactory transduction mechanism has also been proposed to exist only within certain mammals and involves the generation of inositol triphosphate [62]. The signaling pathways above will cause a cation influx *via* the opening of cation channels, which will produce action potentials. This process involves the conversion of a chemical signal, coded by an odorant, to an electronic signal. The electronic signal travels along the nerve cell's axon and is then transmitted to the olfactory bulb, which functions as the bridge between the sense of smell and the cerebral cortex. Signals from the same receptor cells converge onto one Glomeruli in the olfactory bulb, and then converge onto mitral cells. This convergence increases the sensitivity of the olfactory signal relayed to the brain. The olfactory impulses *via* the olfactory tract are then sent to the olfactory cortex where they are projected to the brain's higher cortex, such as the hypothalamus, the hippocampus, which handles conscious thought processes or the limbic system, which creates emotional feelings.

The olfactory system is activated by stimulation from the odorants. This induces a response by the brain cortex that includes the release of the neurotransmitters, such as serotonin, that then stimulates the subsequent pathway. Indeed, this is a chemical-electrical-chemical signal process. In contrast to the current oral drugs used for the treatment of psychiatric disorders, odorants can pass through the blood-brain barrier (BBB) more quickly and efficiently produce a coordinated and speedy response. Consequently, there are many odorants with the potential to be novel treatments for, or that may contribute to the current treatments of, psychiatric disorders. Thus, aromatherapy indeed opens up an innovative window for the treatment of psychiatric disorders *via* therapy involving the CNS.

CONCLUSIONS

Aromatherapy can be defined as the art and science of utilizing naturally extracted aromatic essences from plants to balance, harmonize and promote the health and potency of body, mind and spirit. In the current study, we reviewed previously published literature, as well as unpublished results from our own studies, on the use of aromatherapy for the treatment of psychological disorders. Based on results derived from methylation, siRNA and expression microarray plus gene-specific knockout/ knockdown cell/animal models, we propose that aromatherapy ((C_5H_8)n terpenoids, such as monoterpenoids (n=2) and sesquiterpenoids (n=3)) might behave as antidepressants playing an important role in the neurotransmitter pathways, mainly in 5-HT serotonin system. Indeed, drugs that target the 5-HT system are not only effective as antidepressants, but are also useful as antipsychotics and anxiolytics. Furthermore, the 5-HT system influences other neurotransmitters, such as norepinephrine and dopamine, and is important in regulating mood and behavior. Whereas adequate levels of 5-HT help to maintain a sense of calmness and relaxation, low levels are associated with anxiety, irritability, insomnia, and poor mood. Further research is needed in order to verify whether the molecules in 5-HT pathway are involved in the antidepressant mechanism of aromatherapy, however we cannot ignore the many benefits of aromatherapy for the treatment of psychiatric and mood disorders. The moderate treatment and relatively low incidence of adverse effects make the use of aromatherapy treatment an attractive option. Interestingly, essential oils can produce pharmacologic effects through the sense of smell. This allows for a more rapid onset of effects without the interference of blood brain barrier. Aromatherapy appears to be a simple, economic and low-risk method for the adjuvant treatment of mental disorders. Therefore, it is essential that the indications and applications for their use be determined *via* controlled clinical trials.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

The Xiamen Science and Technology Bureau (Grant No. 3502Z20113013 and No. 3502Z20121153), Natural Science Foundation of Fujian Province (Grant No. 2012J01414), Key Program of Fujian Province (Grant No. 2012Y0064), and the National Natural Science Foundation of China (Grant No. 81101331 and No. 81272445) supported this project.

AUTHORS' CONTRIBUTIONS

Chi-Meng Tzeng had primary responsibility for the dedication in aromatherapy molecular mechanism research, and for the structure and finished manuscript. XN Lv and H J Zhang performed the essential oils research, analysis of the aroma-therapeutic articles and were wrote the primary draft of the manuscript. ZJ Liu provided the essential oils and gave advice regarding the study of aromatherapy on mood disorders.

ABBREVIATIONS

CNS	=	Central nervous system
c-AMP	=	Cyclic Adenosine Monophosphate
BBB	=	Blood-brain barrier
5-HT	=	5-hydroxytryptamine
SSRIs	=	Selective serotonin reuptake inhibitors
SLC6A4	=	Solute carrier family 6 member 4
5-HTT	=	5-HT transporter
MAP	=	Mitogen-activated protein
siRNA	=	Small interfering RNA

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Received: January 14, 2013 **Revised: March 21, 2013** **Accepted: March 22, 2013**