

## ARTICLE

# PHYTO-PHARMACOLOGICAL EFFECT OF NINE MEDICINAL PLANTS AS A TRADITIONAL TREATMENT OF DEPRESSION

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## ABSTRACT

Anxiety, stress and depression are characterized by widespread and highly comorbid psychiatric conditions in the world that are defined as a negative emotional experience and are associated with biochemical, cognitive, behavioral and psychological changes. Herbal medicine has been widely used among suffering and anxiety disorders since ancient times. The modern pharmacological therapy is costly and associated with multiple side effects resulting in patient non-compliance. Thus there is a need to explore alternative therapies particularly from herbal sources as these are cost effective and possess minimal side effects. This review investigates the available studies on the pharmacological effects of some medicinal plants on depression. The studied plants include: *Melissa officinalis*, *Lavandula angustifolia*, *Cinnamomum zeylanicum*, *Viola Odorata*, *Echium amoneum*, *Valeriana officinalis*, *Aloysia triphylla*, *Citrus aurantium* and *Salix aegyptica*. The present article is a comprehensive review of the pharmacological properties, especially anti-depressants, anti-anxiety of nine medicinal plants that could be useful for clinical studies to produce an herbal product which use treat depression.

## INTRODUCTION

The interest in medicinal plant research and the aroma-therapeutic effects of essential oils in humans has increased in recent years, especially for the treatment of neuropathologies with profound social impact such as depression [1]. The medicinal use of essential oils has been known since the early times [2]. Popularly, they are used in the control of emotions and mood, for their sedative, anxiolytic [3], antidepressant effects [4], and anticonvulsant [5] among others [6, 7, 8]. Depression has become a common psychological illness in recent years. According to an investigation by the World Health Organization International Consortium of Psychiatric Epidemiology (WHO-ICPE), 6.3 – 15.7% of the world's population has been estimated to get depression once in their life [9]. It is estimated that by the year 2020, depression will result in the second greatest increase in morbidity after cardiovascular disease, presenting a significant socioeconomic burden. Although a wide variety of antidepressant drugs are available to treat depression, most of the synthetic drugs are not without side effects. Therefore, the search for regularly eaten foods with an antidepressant activity seems to be an essential approach to finding an effective antidepressant treatment without side effects. Modern research on herbal medicine in psychiatry although still in its infancy, has increased in recent years [10].

In Iranian and other traditional medicines, an antidepressant effect has been indicated for some medicinal plants. These include lemon balm (*Melissa officinalis*), lavender (*Lavandula angustifolia*), Cinnamon (*Cinnamomum zeylanicum*), Banafsha (*Viola Odorata*), Echium (*Echium amoneum*), valerian (*Valeriana officinalis*), Aloysia (*Aloysia triphylla*), Citrus (*Citrus aurantium*) and Salix (*Salix aegyptica*) [11, 12]. The association of various plants in a single medication is a relatively common practice in several countries. As examples, in France, Euphytose, an association of *Passiflora incarnata*, *Valeriana officinalis*, *Crataegus oxyacantha*, and three other plants, has been used for its anxiolytic properties [13]. In Chinese therapeutics, the practice of associating various plants with a view to producing one specific therapeutic effect is widely known [14]. This review focuses on the various plants that could be effective in the treatment of depression.

## PHYTOPHARMACOLOGICAL EFFECTS OF NINE MEDICINAL PLANTS

### *Aloysia triphylla*

*Aloysia triphylla* (Verbenaceae) is a perennial, bushy plant, originally from South America, and cultivated in various areas in the Middle East. *Aloysia triphylla* has long been used in traditional medicine. *Aloysia triphylla* has been reported to have a gentle sedative action and helps to counter depression [15]. The plant has tonic effect upon the nervous system and has reputation for soothing abdominal discomfort [16]. The plant has been found to possess antioxidant effect [17]. Phytochemical investigation of the aerial parts of *Aloysia triphylla* has led to the isolation of two compounds artemitin and hesperidin [18]. Artemitin has been claimed that it has an anti-inflammatory effect. Additionally, artemitin was found to induce relaxation in smooth muscle [19]. Hesperidin is a bioflavonoid, which has been reported to possess a wide range of pharmacological properties. It has been reported to have significant anti-inflammatory and analgesic effects [20]. Several mechanisms have been suggested to explain such activity including: inhibition of histamine release [21]; and inhibition of eicosanoid synthesis [22]. Additionally, hesperidin was found to have central nervous system depressant effects [23].

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### *Citrus aurantium*

*Citrus aurantium* L. (Rutaceae), commonly known as sour orange (local name: laranja-amarga, laranja-azedada, laranjacavalo), is used in Brazilian folk medicine and other countries to treat anxiety, insomnia, and as an anticonvulsant, suggesting depressive action upon the central nervous system (CNS), among other properties. Essential oils, especially those of citrus fragrances, are popularly used as therapies for their effects on mood states and depression [24], and the orange essential oil is believed to induce an effect of mental relaxation [25]. A total of 22 phenolic compounds were identified in bitter orange seeds, including hydroxybenzoic acids, hydroxycinnamic acids, flavanones, flavanols, flavonols, flavones, simple phenol and coumarin [26]. Clinical studies suggest that the exposure to the inhalation of various kinds of essential oils is effective in reducing psychological stress, anxiety state, as well as the levels of cortisol in hypertensive patients [27]. The positive effects of essential oils on anxiety and depression symptoms have aroused interest, since they might be an alternative to synthetic substances which induce various side effects such as sedation, memory alterations and interaction with other drugs [28].

### *Echium amoenum*

*Echium (Echium amoenum)* from Boraginaceae family, as an important Iranian traditional remedy, is widely used as a tonic, tranquillizer, diaphoretic, and as a remedy for cough, sore throat, and pneumonia [29]. It is believed that this plant possesses antibacterial, antioxidant, analgesic, anxiolytic, antidepressant and immunomodulatory properties [30; 31]. Also it has been shown that *E. amoenum* aqueous extract was effective in the treatment of obsessive-compulsive disorder [32]. Dried violet-blue petals of *E. amoenum* have been recently recognized as an important source of phenolic compounds like rosmarinic acid, cyaniding, and delphinidin [33]. Cyanidin 3-glucoside, the most common anthocyanin, which is present in petals of *E. amoenum* attenuates PGE2 production and cyclooxygenase-2 expressions by inhibiting activation and translocation of c-Jun and NF-κB factors into nucleus [34]. Also the neuroprotective activity of cyanidin 3-glucoside has been investigated by Min et al. They suggested that the beneficial effect was related to attenuation of brain superoxide levels resulted from blocking apoptosis-inducing factor release in mitochondria [35].

### *Lavandula angustifolia*

Lavender (*Lavandula angustifolia*) is a famous herb that has a long history in folk medicine and is still therapeutically used today. The essential oil obtained by steam distillation from the fresh flowering tops of this plant is often used in aromatherapy as a relaxant [36]. Inhalation of the vapor of the lavender essential oil and its main constituent, linalool, has shown sedative effects in both human and animal studies [37]. Other pharmacological effects of this oil, including anticonvulsive [38] anxiolytic [39], antidepressant [40], and anticonflict effects [41], have also been reported. On the other hand, lavender is also used as a tea infusion (i.e., aqueous extracts) to treat restlessness, insomnia, and nervous disorders of the stomach and intestines [42]. Furthermore, lavender contains aqueous phenolic constituents, such as hydroxycinnamic acids and flavone glycosides [43], which have been associated with the antioxidant activities of Lamiaceae plants including lavender [44].

### *Melissa officinalis*

*Melissa officinalis* (Lamiaceae) or lemon balm is an herbal medicine native to the eastern Mediterranean region and western Asia. This plant is known as "Badranjboyeh" in Iran, and grows widely in provinces of Tehran, Golestan, Azarbayjan, Lorestan and Kermanshah [45]. Dried or fresh leaves and top aerial section of the plant are the parts which are used as medicine [45]. Lemon balm has been traditionally used for different medical purposes as tonic, antispasmodic, carminative, diaphoretic, surgical dressing for wounds, sedative-hypnotic, strengthening the memory, antidepressant and relief of stress-induced headache [46]. In Iranian traditional medicine, lemon balm has also been used in treatment of irritability and nervousness in young girls and women, lack of interest and energy, and depression [47]. Ibn Sina (Avicenna), the well-known Iranian scientist, recommended *Melissa officinalis* for above indications. The main components of the essential oil are 39% citronellal, 33% citral (citronellol, linalool) and 2% geranial. In addition, this oil contains such as threeterpinene, phenol carbon-acid (rosmarinic acid), and flavoglycoside acids in low ratio. Furthermore, it is stated that the essential oil of lemon balm which is, used in aromatherapy, may be beneficial for mild depression (3). The leaves of *Melissa officinalis* also known as lemon balm, are used in traditional medicine to prepare a tea for its nerve calming and spasmolytic effects [48] although there are a great variety of phytopharmaceutical preparations containing this plant or its extracts. Furthermore, this plant is used by food industry to flavor different products due to its particular taste. The number of people suffering from neurological disorders has lately increased worldwide, specially in the developed countries [49]. Between them, neurodegenerative diseases (Parkinson, Alzheimer) as well as psychiatric ones (anxiety and depression) are the most common [50].

### *Salix aegyptiaca*

*Salix aegyptiaca* commonly known as Musk Willow is a flowering plant and generally cultivated in some provinces of Iran for hedge and ornamental purposes [51]. Individual flowers are either male or female, but only one sex is to be found on one plant, so both male and female plants must be grown if seed is required and are pollinated by bees. The male inflorescences distillate of the plant has long been used in Iranian folklore medicine as cardiostimulant, treatment of anemia, vertigo and depression, as well as a fragrance additive. Phenolic compounds from the extracts indicated the presence of gallic acid, caffeic acid, vanillin and p-coumaric acid, myricetin, catechin, epigallocatechin gallate, rutin, quercetin as well as salicin. The aqueous extract and essential oil of these inflorescences are also being used in confectionary, flavorful syrups and especially in the preparation of a local candy (Noghl-e Urmia) [52]. In addition, *S. aegyptiaca* is used as laxative, cardioprotective, nervous, sedative, hypnotic, somnolent, aphrodisiac, orexigenic, carminative and gastroprotection. The decoction of *S. aegyptiaca* leaves in honey still is used as a nervonic functional food [52].

### *Valeriana officinalis*

*Valeriana officinalis* (Valerianaceae family) is a medicinal plant used in complementary and alternative medicine for its sedative and anxiolytic properties [53]. There are three main chemicals that are thought to be the active components of the plant. These are the essential oils, valerenic acid and valenol, valepotriates, and a few alkaloids. Valerian's effects on the central nervous system have been well documented and attributed to many of its active compounds: valepotriates, baldrinals, valerenic acid, valerenal and valeranone, and other constituents in the essential oils [53]. Consequently, the therapeutic properties of *Valeriana officinalis* have yet to be conclusively demonstrated [54]. The pharmacological effects attributed separately to each plant of a phytotherapeutic product – CPV (dry extract of *Crataegus oxyacantha* L., *Passiflora incarnata* L., and *Valeriana officinalis* L.) are well described in the literature. For instance, *P. incarnata* exerts anxiolytic, sedative and anticonvulsant actions [55], *C. oxyacantha* possesses cardiostimulant, antiatherogenic, and antioxidant effects, which would enhance its action on atherosclerosis [56] and *V. officinalis* was utilized traditionally as a sedative for light insomnia, in addition to being indicated for its anxiolytic properties when administered in smaller doses [57]. Root extracts from *Valeriana officinalis* are popular herbal supplements and are widely used in the treatment of sleep disorders, anxiety, depression and epilepsy. Sleep disturbance can be associated with poor work performance, increased anxiety and depression, poor cognitive functioning, and impairment of overall QOL [58].

### *Viola odorata*

*Viola odorata* is a species of the genus *Viola* native to Europe and Asia, but has also been introduced to North America and Australasia. It is commonly known as wood violet [59], sweet violet, English violet, common violet, or garden violet. The sweet scent of this flower has proved popular throughout the generations particularly in the late Victorian period, and has consequently been used in the production of many cosmetic fragrances and perfumes [59].

In the traditional system, it has been used in anxiety [60], insomnia and to lower blood pressure [61]. Violet is mainly used as an herbal remedy in cases of various respiratory ailments. It can be very beneficial in treatment of congestion, coughs and sore throat. Recent studies have shown the presence of glycoside of salicylic acid in Common Violet leaves, which explains its efficient use in cases of headaches and body pains. Syrup made from Common Violet's flower has anti-septic, anti-inflammatory, laxative and expectorant properties. It can be helpful in cases of various respiratory conditions, but also in treatment of headaches, insomnia, dizziness and exhaustion [62]. *Viola* contains alkaloid, glycoside, saponins, methyl silylate, mucilage and vitamin C. The plant has been reported to possess antioxidant and diuretic activities along with other beneficial effects but no study has been found regarding its blood pressure lowering or lipid-lowering activity [61].

### *Cinnamomum zeylanicum*

Cinnamon and its extract, irrespective of source, have been associated with a variety of health beneficial effects, including anti-microbial, anti-viral, antioxidant, and antidepressant activities. Many of the corresponding bioactivities are possibly attributed to cinnamaldehyde, a major constituent of the essential oil responsible for the flavor and aroma of whole cinnamon. In addition, a number of polymeric polyphenol molecules known as proanthocyanidins are present in the aqueous extract that are likely responsible for the majority of the antioxidant properties of cinnamon [63]. While the health-beneficial effects of bioflavonoids in general are traditionally thought to be due to their antioxidant activity, proanthocyanidins exhibit other properties that may be important for their bioactivities [64]. Cinnamon bark contains procyanidins and catechins. The components of procyanidins include both procyanidin A-type and B-type linkages. These procyanidins extracted from cinnamon and berries also possess antioxidant activities [65]. Cinnamon can also improve the health of the colon, thereby reducing the risk of colon cancer. Cinnamon is a coagulant and prevents bleeding [66]. Cinnamon also increases the blood circulation in the uterus and advances tissue regeneration. This plant plays a vital role as a spice, but its essential oils and other constituents also have important activities, including antidepressant, antimicrobial, antifungal, antioxidant, anti-diabetic and anti-inflammatory [66].

## FUTURE DIRECTION

Considering therapeutic potential of these nine medicinal plants in terms of their efficacy and adaptability is such that combination of them as one organic product can be noticed in future, since depression is becoming more epidemic around the world especially in developing countries as an organic product by using local knowledge can reduce many problems associated with the use of chemical drugs and their side effects to a large extent.

**Table 1:** Nine medicinal plants with evidence of their activities

Plant	Plant part used	Bioactive compounds	Screened activity
<i>Aloysia triphylla</i>	Roots	Flavonoids (Artemitin and Hesperidin)	Antidepressant, anti-inflammatory [23]
<i>Citrus aurantium</i>	Flowers	phenolic compounds like flavanone glycosides, hydroxycinnamic acids	Antidepressant, anticonvulsant, antianxiety, antioxidant [24]
<i>Echium amoneum</i>	Leaves and flowers	phenolic compounds like rosmarinic acid, cyanidin, and delphinidin	Antidepressant, anti-hyperlipidemia, anti-cholesterol, antibacterial, anti-diabetic and antioxidant [30, 31]
<i>Lavandula angustifolia</i>	Flowers	phenolic compounds like hydroxycinnamic acids and flavone glycosides	Antidepressant, anticonvulsive, anxiolytic, antioxidant [40]
<i>Melissa officinalis</i>	Leaves and stems	Citronellal, citral (citronellol, linalool), geranial, threeterpinene, phenol carbon-acid (rosmarinic acid), and flavonglycoside acids	Antidepressant, antimicrobial, antispasmodic, antioxidant [47]
<i>Salix aegyptiaca</i>	Leaves and stem bark	phenolic compounds like gallic acid, caffeic acid, vanillin and <i>p</i> -coumaric acid, myricetin, catechin, epigallocatechin gallate, rutin, quercetin and salicin	Antidepressant, antioxidant, anti-vertigo, anti-anemia [52]
<i>Viola odorata</i>	Leaves and flowers	alkaloid, glycoside, saponins, methyl silylate, mucilage and vitamin C, Cycloviolacin O2 (CyO2)	Antidepressant, anti-hyperlipidemia, anti-cholesterol, anti-blood pressure, anti-cancer and anti-tumor [60]
<i>Valeriana officinalis</i>	Leaves	alkaloid, glycoside, saponins, methyl salicylate and mucilage	Antidepressant, antioxidant, anti-inflammatory, laxative, anti-septic, anti-hyperlipidemia [57]
<i>Cinnamomum zeylanicum</i>	Stem bark and leaves	Eugenol. Cinnamaldehyde, camphor, procyanidins and catechins	Antidepressant, antimicrobial, antioxidant, anti-diabetic and anti-inflammatory [66]

### CONFLICT OF INTEREST

There is no conflict of interest.

### ACKNOWLEDGEMENTS

Author is grateful to Parsiteb Kohan Company (Paprika) for their support and providing necessary facilities to carry the research.

### FINANCIAL DISCLOSURE

None

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