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The Role of Mufarrehat (Exhilarants) in the Management of Depression: An Evidence Based Approach

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Abstract

Depression is a most common, debilitating and life threatening illness and most serious mental health problem that people face nowadays. It is characterized by change in mood, lack of interest in surroundings, feeling of sadness, gloominess or melancholy. According to WHO report, depression is the fourth leading causes of disability worldwide with a prevalence of approximately 5% in general population. In Unani perspective, depression is not a disease rather it is a symptom or group of symptoms of *Malankholia* (Melancholy) in which the mental functions of the individual are deranged leading to constant grief, fear and dubious aggression. Unani scholars consider *Ghair Tabayi Sauda* (Abnormal black bile) as the cause and basis of psychological and psychiatric disorders e.g. anxiety, depression, melancholy etc. *Mufarrehat* (exhilarants) are the most critical requirement in the essential medicament of such diseases. Unani scholars have strongly advocated the use of *Mufarrehat* (Exhilarants) in psychiatric diseases after evacuation of vitiated humors from the body. Some preclinical studies amply prove that many plants, which are in vogue since ages for the treatment of psychological disorders, influence the central nervous system and exerted many pharmacological effects hitherto unknown to the medical realm. This review will highlight the central nervous effect of Unani antipsychotic drugs with special reference to antidepressant effect of *Mufarrehat* thus validating the classical Unani concept.

Keywords: Mufarrehat; Exhilarant; Melancholia; Depression; Antidepressant; Unani medicine

Introduction

Depression is a common, debilitating, life threatening and serious mood disorder with an increasing morbidity and mortality that affects more than 300 million individual worldwide. It interferes with an individual's thoughts, behavior and feelings and affects a person's ability to work and form relationships and destroy their quality of life. It is the fourth leading cause of disability, which contributes a major role in increasing the overall global burden of disease. It can lead to suicide if left untreated and is responsible for 850,000 deaths every year [1-3]. Depression is characterized by change in mood, lack of interest in surroundings and enjoyment, feeling of sadness, gloominess or melancholy [1,4]. Many depressed individual experience anxiety symptoms, disturbed sleep, poor concentration, feelings of guilt or low self-worth and increased or decreased appetite, and may have even medically unexplained symptoms [1].

Mental depression is classified into unipolar and bipolar depression. Unipolar depression is more common and account nearly 75% of cases, in which mood swings are always in the same direction. It is accompanied by symptoms of anxiety and agitation, shows a non-familial pattern and closely related to stressful life events. Bipolar depression is less common (about 25% of cases) which shows a familial pattern, appears in early adulthood and usually have no relation with external stress. In this type, mood swings are bidirectional and results in swinging depression and mania over a period of a few weeks [5]. The exact etiology of depression is still remains obscure, but the most popular theory is the decrease in the neurotransmitter levels in the brain such as noradrenaline, 5-hydroxytriptamine (5-HT) and dopamine. However, recent studies have also shown the involvement of oxidative stress in the phenomenon [2,4].

Although there are known, effective treatments for depression in conventional system of medicine and a number of synthetic drugs such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are available and being used as standard treatment for clinically depressed patients, one may not ignore the possible adverse effects associated with these antidepressant medication such as dry mouth, fatigue, anxiety agitation, drowsiness, gastrointestinal or respiratory problems, and cardiac arrhythmias [5]. Further, it is very difficult in predicting the patients' response to treatment. It has been reported that out of three patients only two cases respond to any antidepressant treatment, and of these, it is presumed that one would probably have placebo effect [4]. These conditions create demand of an alternative medicament with minimal adverse effects to combat with this situation and to fill the lacunae in the current treatment option. Keeping in view, scientists are turning their attention towards indigenous systems of medicine to explore and develop newer anti-depressant drugs from plants and their active metabolites. Many plants have been used since ages for the treatment of depression and other psychiatric diseases in Unani system of medicine and many of these have been reported to have a rate of efficacy comparable to the conventional treatment with fewer side effects. This review will highlight the central nervous effect of Unani antipsychotic drugs with special reference to antidepressant effect of *Mufarrehat* (exhilarants) thus validating the classical Unani concept.

Depression in unani perspective

Psychiatric diseases were well recognized in the ancient Unani world. Melancholy and hysteria were well known to Egyptian and

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Sumarian physician as early as 2600 BC. The psychiatric nosology is discussed comprehensively in Unani classical texts under the title of *"Amraaz-e-Nafsani"* (psychiatric disorders) where all the diseases are classified as syndrome rather than an individual disease entity [6]. In the similar fashion, depression is not mentioned in Unani classical texts as an individual disease entity rather it is mentioned as a symptom or group of symptoms of *Malankholia* (Melancholia) in which the mental functions of the individual are deranged leading to constant grief, fear and dubious aggression. The patient find himself/herself deserted and occupied by loneliness and some patients experience delusion and hallucination [7,8]. Unani scholars consider *Ghair Tabayi Sauda* (Abnormal black bile) as the main cause and basis of psychological and psychiatric disorders e.g. anxiety, depression, melancholia etc. whether it is associated with the *Ehteraq* (combustion) of *Dam* (blood), *Balgham* (Phlegm), *Safra* (bile) or *Sauda* (black bile) itself [9,10]. Ibn-e-Sina has stated in his renowned book Al-Qanoon fit-Tibb, that the *Mizaj* (temperament) of *Khilt-e-Saudawi* (Black bile) is *Barid Yabis* (cold and dry) which is contrary to the *Mizaj* of *Rooh-e-Dimagi* (temperament of mental/vital spirit) thus resulting in derangement of *Rooh-e-Dimaghi* and leading to *Khauf* (Fear) [10]. Describing pathogenesis of *Malankholia,* Ibn-e-Hubal Baghdadi has stated that the interaction of *Ghair Tabai Sauda* with *Rooh-e-Nafsani,* results in *Kodoorat* (murkiness), *Taariki* (darkness), *Boroodat* (coldness) and *Yaboosat* (dryness) in the brain, which is against the *Mizaj* of *Rooh-e-Nafsani* and the brain as well, thus leading to insanity and thinking disability in the affected persons [9].

Management

The Unani system of medicine is replete with many treatment regimens for psychological disorders. The management of this malady involves a threefold strategy [10-13].

1. ***Nafsiyati Tadabeer:*** Distracting the mind through adaptive changes and distracting methods are the basic principle of treatment to make the patients comfortable and happy. Adaptive changes are living in clean, well lit house, which has provisions for fresh breezes of air, wearing white or pastel shades, ensuring comfort and entrusting with responsibility. Distracting methods include visiting hill stations and parks, viewing plays, hearing pleasant music, being in company of religious people, listening religious sermons and interesting stories, reading books and inculcating hobbies etc.

2. ***Tanqiya-e-Mawad and Tarteeb:*** Evacuation and excretion of *Ghair Tabai Sauda* (pathological melanchole) through *Munzijat* (concoctive) and *Mushilat* (purgatives) followed by *Tarteeb* (moisturizing) is the second line of treatment for psychological disorders. *Tarteeb* is always essential after *Tanqiya,* to check and reduce the dryness, produced by *Tanqiya*. Ibn-e-Sina has stated that due attention must be paid towards *Tarteeb-e-Mizaj* (moisturizing the temperament) in cases of *Malankholia* and the sleep is important and integral part of the treatment because it produces *Rotoobat* (moisture) in the brain.

3. ***Taqwiyat-e-Qalb:*** Strengthening the heart through *Mufarrehat-e-Qalb* (exhilarants) is necessary and essential line of treatment after evacuation of vitiated humors from the body as stated by various Unani scholars.

Role of *Mufarrehat* (exhilarants)

Mufarrehat (exhilarants) are one of the most critical requirements in the essential medicament of psychological disorders. Unani scholars have strongly advocated the use of *Mufarrehat* (Exhilarants) in psychiatric diseases after evacuation of vitiated humors from the body [10-13]. The reason behind the phenomenon is the strong relationship between the heart and the brain. Whenever brain is affected by *Boroodat* (coldness) and *Yaboosat* (dryness), the temperament of heart is also get affected and the vice versa. Ibn-e-Sina has stated that *Su-e-Mizaj-e-Qalb* (alteration of heart temperament) affects *Rooh-e-Nafsani* leading to *Fasad* (vitiation) of *Rooh-e-Haiwani* resulting in *Fasad* in the temperament of brain and changes it into melancholic temperament. He added to it that the causes of *Boroodat* and *Yaboosat* that affects the brain, produced not only in the heart but it might be produced in other parts of the body also. However, the heart always has a strong association with other parts in producing such causes. Thus, the treatment of heart is essential with the treatment of diseased brain. The clean, furbished, lustrous and exhilarant blood of heart is capable of fighting against the deprived temperament of brain and to restore its proper functioning [10]. *Mufarrehat* are the drugs that clean, furbish, lengthen and improve the quality of *Rooh-e-Qalbi* and restore the normal temperament of heart [14], resulting in restoration of normal brain temperament with a feeling of ecstasy.

Scientific evidences of *Mufarrehat*

Many plants are in vogue as *Mufarrehat* in single or compound forms since ages for psychological disorders. These include, Zafran (*Crocus sativus*), Sumbul-ut-Teeb (*Nordostachys jatamansi*), Gauzaban (*Borago officinalis*), Badranjaboya (*Melissa parviflora*), Faranjamushk (*Ocimum gratissimum*), Tukhm-e-Karafs (*Apium graveolens*), Ward (*Rosa demescena*), Jaifal and Javitri (*Myristica fragrance*), Rehan (*Ocimum sanctum*), Qaranfal (*Syzygium aromaticum*), Heel Khurd (*Elettaria cardamomum*), Taj (*Cinnamomum casia*), Saad kufi (*Cyperus rotundus*), Ood (*Aquilaria agallocha*), Bahmen (*Centaurea behen*), Ustokhuddus (*Lavendula steochas*), Kafoor (*Cinnamomum camphora*), Sandal safed (*Santalum ulbum*), Zaranbad (*Zingiber zerumbet*), Shaqaqul (*Asparagus racemosus*), Tamar hindi (*Tamarindus indicus*), Anar (*Punica granatum*), Gul-e-gudhal (*Hibiscus rosa sinensis*), Gul-e-Nilofer (*Nymphaea alba*) etc. [14-16]. Of these, many have been reported to have potent antidepressant and other neuropharmacological activities.

Badranjaboya (*Melissa parviflora,* family - Lamiaceae)

Badranjboya, commonly known as gentle balm is an aromatic perennial herb, traditionally used as tranquillizer, nervine relaxant and sleeping aids. It has been used for the treatment of neuralgia, anxiety-induced palpitation, insomnia and tension-relating disease such as migraine. It is widely valued for calming properties. Anxiolytic activity of various extracts of the plant was evaluated using elevated plus-maze (EPM) apparatus and light and dark test model of anxiety in Wistar rats. Methanol extract of *M. parviflora* exhibited significant anxiolytic activity (100 and 200 mg/kg, p.o.) with respect to vehicle treated control and diazepam (2 mg/kg, p.o.) as positive control. Therefore, *M. parviflora* could serve as a new approach for the treatment of CNS disorders like anxiety [17].

Gul-e-Gauzaban (*Borago officinalis*, family - Boraginaceae)

Gauzaban is an annual herb with nutritional value, used in traditional medicine and culinary uses in some countries. It has been reported that borage has antipyretic, aphrodisiac, antispasmodic, demulcent, antihypertensive and diuretic effects. The products of Borage are used for the treatment of bronchitis, palpitations, cramps and diarrhea. Anxiolytic-like activity of Borage flowers extract was evaluated using an EPM test in male Wistar rats. Acute IP injection of

Borage extract (50, 100, 200 mg/kg) before an EPM trial significantly increased the time spent in open arms and percentage of open arms entries, whereas, the extract showed no effect on the number of closed arm entries. The results indicated that IP injection of Borage extract might have an anxiolytic potential in rats [18].

Sumbul-ut-Teeb (*Nordostachys jatamansi,* family - Valerianaceae)

Sumbul-ut-Teeb has a long history of use as ethnomedicine, used to treat epilepsy, hysteria and syncope, helps to promote physical and mental health, augment immunity and has shown potent free radical scavenging activity. It has also shown marked tranquilizing activity, as well as hypotensive, hypolipidemic, anti-ischemic, antiarrhythmic, hepatoprotective, anticonvulsant, radioprotective and neuroprotective activities. Ethanolic root extract of *N. jatamansi* at the dose of 200 mg/kg orally was administered in electron beam radiated mice for screening of its antidepressant effect using Forced Swimming Test (FST) and Tail Suspension Test (TST). A significant reduction in immobility time was observed in the electron beam radiated mice treated with *N. jatamansi* ethanolic root extract in both tests when compared to non-treated electron beam radiated mice. The data suggest that the depression caused due to exposure of low levels electron beam radiation can be checked by the administration of ethanolic root extract of Jatamansi [19]. Ethanolic extract of *N. jatamansi* at the oral dose of 100, 200 and 400 mg/kg for 14 days produced significant antidepressant like effect in swiss young albino mice, comparable to imipramine (15 mg/kg, po) and sertraline (20 mg/kg, po) in both TST and FST. However, no significant change was observed on locomotor activity of mice treated with ethanolic extract (200 mg/kg, po) as compared to control. The extract decreased the whole brain MAO-A and MAO-B activities as compared to control, thus increased the level of monoamines. Further, the antidepressant effect of extract was also significantly reversed in animals pretreated with baclofen ($GABA_B$ agonist) in tail suspension test. The antidepressant effect of Jatamansi may be due to interaction with $GABA_B$ receptors, resulting in decreased level of GABA in mouse brain. The data suggests that *N. jatamansi* may have promising value for the management of depression [20].

Tukhm-e-Karafs (*Apium graveolens*, family - Apiaceae)

Karafs, commonly known as celery is a biennial herb that has been used consistently throughout history in medical preparation, food flavouring and preparation [21]. The plant has a broad spectrum of medicinal use as an aphrodisiac, anthelmintic, antispasmodic, carminative, diuretic, emmanogogue, laxative, sedative, and stimulant. It has many pharmacological studies as antifungal, antihypertensive and hypolipidemic, diuretic, anticancer and many more. Epidemiological evidence supports a relationship between ingestion of celery and a myriad of beneficial effects, ranging from cardioprotective to anticancer properties [21,22]. Methanolic extract of *A. graveolens* seeds (100, 200 mg/kg) was investigated and showed significant anti-depressant effect in two behavioral models *viz.* forced swim test and tail suspension test. The anti-depressant effect of the extract was comparable to imipramine (20 mg/kg) in a dose dependant manner [21].

Zafran (*Crocus sativus* Linn, family- Iridaceae)

Saffron is an herbaceous perennial-cormous plant, which is believed to show many pharmacological actions. The plant contains various important chemical constituents like crocin, crocetin, safranal and picrocrocin. These constituents possess a wide range of pharmacological activities, i.e., antinociceptive, anti-alzheimer's, anti-parkinsonian, learning or memory improving properties, anti-oxidant activity, anxiolytic activity etc. Saffron and its active constituents like crocin and safranal have been reported to have antidepressant activity, which is probably due to uptake inhibition of dopamine, norepinephrine and serotonin. Antidepressant activity of Safran stigma was evaluated to compare its effect with standard imipramine and to investigate its combined effect with submaximal dose of imipramine in mice using FST and TST. Saffron alone (at the doses of 200, 400 and 800 mg/kg i.p) as well as in combination with submaximal dose (7.5 mg/kg) of imipramine showed significant reduction in immobility time when compared to control and it was comparable to standard drug imipramine (15 mg/kg) in both FST and TST [23]. A clinical study result showed significant anti-depressant effect of Saffron (30 mg/day TDS and BD) in mild to moderately depressed adult patients comparable to imipramine (100 mg/day TDS) and Fluoxetine (20 mg/day BD) [5].

Rehan (*Ocimum Sanctum,* family - Labiatae)

Tulsi (Holy Basil) has been recognized for thousands of years to be one of India's greatest healing herbs and used successfully in the treatment and prevention of many stress disorders. It enhances general health and well-being, having positive overall effects on the body and mind. The plant has hypoglycemic, hypolipidemic, antioxidant, adaptogenic, antiepileptic, hepatoprotective, antifertility, anticancer, antiasthmatic, antiemetic, diaphoretic, radioprotective, antiviral, analgesic and anti-inflammatory properties. It is also effective against dementias, anti-stress, Alzheimer's disease and anxiety. It helps in relieving the anxiety and agitation associated with depression and also showed anti-aggressive and calming effect. Ethanolic extract of Tulsi leave (at doses 4 mg/kg and 8 mg/kg) significantly reduced the immobility time in both FST and TST model. Methanol extract from roots (at dose 400 mg/kg, i.p.) showed increase in swimming time, suggesting its antidepressant activity. Etahnolic extract of leaves significantly decreased the immobility time in forced swimming test in rats and mice. This action was blocked by Haloperidol and Sulpiride, suggesting a possible action involving dopaminergic neurons [3,5].

Jaifal (*Myristica fragrans*; family - Myristicaceae)

Nutmeg is widely used in a variety of ways and for various purposes. Dating back to the 16th century, nutmeg has been known for its psychoactive properties, which include anxiogenic and hallucination. Medicinally, nutmeg is known for its anti-inflammatory and antithrombotic, as well as anti-rheumatic, carminative and stimulant properties. In pregnancy and lactation, nutmeg is used in traditional medicine practice for antenatal and postnatal treatment. Nutmeg extract was investigated for its antidepressant effect on rats using FST, Reserpine Reversal Test (RRT), Haloperidol-Induced Catalepsy (HIC), and Pentobarbitone Sleeping Time (PST). A significant reduction in immobility time in FST, RRT, and protection against HIC was observed upon administration of Nutmeg extract (500 mg/kg p.o.) and imipramine when compared to the control group. The extent of decrease in immobility time in case of Nutmeg extract was found to be very higher than that of imipramine in FST and RRT. The protective effect of Nutmeg extract against Haloperidol-induced catalepsy was comparable to imipramine. Both, the dopamine facilitatory and anti-oxidant properties of Nutmeg extract might have attributed to its anticataleptic effect [4].

Franjamushk (*Ocimum gratissimum*, family - Lamiaceae)

Faranjamushk is an aromatic medicinal plant, being used extensively for the treatment of epilepsy, fever, diarrhoea, mental illness, fungal

infections, cold and convulsion. Oral administration of Leaf extracts of *O. gratissimum* and the essential oil showed anticonvulsant, anxiolytic, CNS depressant, and antinociceptive activities respectively. Essential oil of *O. gratissimum* was investigated to assess the sedative, anxiolytic-like, antidepressant-like and motor coordination effects, in mice using the open field test, light/dark box test, tail suspension test and Rota-rod test. Upon inhalation, *O. gratissimum* essential oil showed significant sedative, anxiolytic and antidepressant-like effects, and did not cause any detrimental effects on motor coordination [24].

Ward (*Rosa damascene,* family - Rosaceae)

Rose is a well-known ornamental plant referred to as the king of flowers. It has been used extensively for the treatment of abdominal and chest pain, digestive problems, menstrual bleeding and strengthening the heart. Also used as a cough remedy and as a gentle laxative. Rose oil heals depression, grief, nervous stress and tension. Besides many pharmacological activities, rose was also reported for its anti-depressant activity. Rose contains several components such as flavonoids and kaempefrol, responsible for its antidepressant activity. Antidepressant activity of aqueous extract of rose (at 20 mg and 40 mg/kg) was investigated in albino mice using FST to compare its effect with imipramine. The extract significantly decreased the immobility time in mice showing dose dependant antidepressant activity comparable with imipramine [25].

Saad Kufi (*Cyperous rotundus,* family - Cyperaceae)

Cyperus rotundus in an important traditional medicine which is widely used as anti-inflammatory, antidepressant, antipyretic, analgesic and antiemetic remedy, for dysentery and gynaecological diseases. Several components have been isolated from the rhizomes of *C. rotundus* which are responsible for various observed pharmacological studies [26]. Ethanol extract and its fractions of C. rotundus were evaluated for antidepressant activities in mice. Three new phenolic glycoside components rotunduside D (1), rotunduside E (2), and rotundoside F (3) were isolated and screened for potential antidepressant activity. In the despair mice models, rotunduside F (3) showed significant antidepressant activity at the dosage of 50 mg/kg, which was close to the positive control fluoxetine (20 mg/kg) [27]. Two new cycloartane glycosides, cyprotusides A (1) and B (2) showed significant antidepressant activity in the despair mice models [28]. Two new iridoid glycosides, named rotunduside G (1) and rotunduside H (2) was isolated from the rhizomes of *Cyperus rotundus* and both components showed significant antidepressant activity [29].

Besides these, many more *Mufarrehat* as well as other drugs that have been used in the unani system of medicine since ages for the treatment of psychological disorders have been reported for their neuro-pharmacological activities. These include Qaranfal (Syzygium aromaticum) [30], Ood (*Aquilaria agalocha*), Sandal (*Santalum album*) [31], Anisoon (*Pimpinella anisum*) [2], Kaiphal (*Myrica nagi*) [32], Badiyan (*Foeniculum vulgare*) [33], Bahmen (*Centaurea behen*) [34], Bazarulbanj (*Hyoscyamus niger*) [35], Habb-ul-Ghar (*Laurus Nobilis*) [36], Halela (*Terminalia chebula*) [37], Ustokhuddoos (*Lavendula steochas*) [38], Kalaunji (*Nigella sativa*) [39], Sibr (*Aloe barbadensis*) [40] etc.

Conclusion

Depression is a most common, debilitating, life threatening illness and one of the most leading causes of disability worldwide which affects not only the affected person but his/her family and society as well. Though effective medications are available in conventional system, adverse effects produced by their use may not be ignored. Unani system of medicine is replete with the treatment of depression and other psychological disorders. Use of *Mufarrehat* is the integral part in treating patients with psychological disorders such as anxiety, depression and malankholia. Many *Mufarrehat* and other drugs, being used since ages for psychological disorders, have already been reported for their various neuropharmacological activities. Aforesaid preclinical/clinical studies attest that *Mufarrehat* modulate the physiology of CNS and have a potential clinical value for use in the management of psychological disorders, thus validating the age old theory of Unani scholars.

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