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PHARMACOLOGICAL ROLE OF *HABB-I-SHIFA* IN AMELIORATING ADDICTION OF OPIOIDS: A REVIEW

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ABSTRACT

Background: *Habb-i-shifa*is an important pharmacopoeial Unani formulation that promises to be beneficial to opium addicts and helps to alleviate withdrawal symptoms. Various scientific researches done demonstrated positive results of *Habb-i-shifa* in alleviating morphine withdrawal syndrome in rats and Swiss mice, hence validating the Unani Medicine claim that *Habb-i-shifa* is an important medicine to be used in the treatment of opioid withdrawal. Drug addiction, often known as drug abuse disease, is a longstanding issue. Currently, recreational usage or peer modelling can lead to substance dependence. The magnitude of the addiction problem grows exponentially in the presence of stresses such as broken homes, unemployment, occupational stress, and so on. The de-addiction procedure is used to eliminate a person's desire for the drug. It is a painful process since the consequences of withdrawal cause a person to return to the drugs repeatedly. The current paper attempts to conduct a full review of *Habb-i-shifa*'s opiate de-addiction impact in light of Unani classical literature. Our goal is to investigate the available literature on the use of Unani medicine for addiction treatment.

KEYWORDS: *Habb-i-shifa*, Opioid abuse, *Dhatūra*, Unani medicine

INTRODUCTION

Substance abuse and Dependence

Substance abuse is the term used to describe the dangerous or damaging use of psychoactive substances, such as illegal drugs and alcohol[1]. Substance use is defined as using a substance to treat a disease, prevent a disease, or enhance one's health. Substance abuse is also known as drug abuse. Drug abuse, on the other hand, occurs when a drug is used for non-medical purposes, in quantities, potencies, or ways that impair a person's ability to function physically or mentally. In 1956, the American Psychiatric Association and the World Health Organisation defined drug abuse as "the illegal use of any pharmaceutical or naturally occurring substance to alter one's feelings, thoughts, or behaviour without being aware of or respecting the detrimental physical and mental side effects that are caused"[2]. Only 15–16% of users develop an addiction within 10 years of their first use, even for a highly addictive substance like cocaine[3]. It is nevertheless true that drug usage does not always result in addiction, even if a significant portion of people do develop an addiction. Drug usage is only one aspect of addiction. It is specifically defined as an obsessive pattern of drug-taking and drug-seeking behaviour that takes precedence over the majority of other activities[4].

Causes of Substance abuse

The causes may vary from person to person and more than one cause could be responsible for it. Causes of substance abuse can be as follows[5]:

1. Social factors
2. Psychological factors
3. Biological factors

Opioid Dependence

Drug misuse and opioid dependence are important public health issues around the world. There are numerous therapeutic strategies for substance use disorders[6]. Because patients with substance use disorders who are receiving standard pharmacological therapies may still relapse, incorporating alternative treatments such as medicinal plants into addiction treatment may have positive results[7]. These medicines are commonly used as prescription pain relievers. Many people begin taking these drugs to deal with a specific medical concern, such as painkillers after an injury or surgery. However, over time, higher doses are required to achieve the same level of pain relief, and people begin abusing medication that was not prescribed for them in order to get high, relieve tension, increase alertness, or improve

concentration. Some users can become physically dependent, experiencing withdrawal symptoms such as nausea, muscle cramping, depression, agitation, anxiety, and opiate cravings if they try to quit. Drooping eyes, constricted pupils even in low light, abrupt itching or flushing, slurred speech, drowsiness, loss of energy, inability to concentrate, lack of desire, decline in work or school performance, and disregard of friendships and social activities are all signs of opioid misuse.Substance use disorder is a brain disease that affects a variety of brain circuits, including those involved in reward and motivation, learning and memory, and inhibitory control over behavior[8]. Substance use disorders are chronic relapsing illnesses that cause severe morbidity and impairment in psychosocial functioning[9,10]. Drug abuse and addiction are disorders that result in negative outcomes from the use of chemical substances. Neuroadaptation underpins both the emergence of withdrawal symptoms and the possibility of recurrence[11]. Opium addiction and dependence are linked to its intense cold *mizāj* (temperament), which can lead to cravings for bigger doses. The management of opioid addiction has been centered on the slow and steady lowering of opium doses or the use of opiate alternatives with lower dependency or tolerance. There have been several published methods for effectively curing dependence. The main complications associated with opium addiction include severe withdrawal symptoms and relapse of addiction. The management's success is determined by the extent to which withdrawal symptoms are controlled during opium abstinence[12].

Neurobiology of Addiction

Drug addiction has been described as a complicated and chronic illness process affecting the brain and influenced by genetic, developmental, and environmental variables. Dopamine (DA) is at the center of drug reward[13,14]. The most constant and persistent result in drug addiction is that misused substances stimulate the mesolimbic dopamine pathway, reinforcing both pharmaceutical and natural rewards. Dopaminergic neurons in the ventral tegmental area (VTA) send axonal projections to terminal fields in the nucleus accumbens (NAc) and prefrontal cortex[15].

Opioids, alcohol, nicotine, cannabis, and psychostimulants all stimulate this pathway, increasing synaptic dopamine (DA) levels. All of these compounds have specific brain receptors, and the end result is an increase in dopamine levels in the mesolimbic pathway. Opiates indirectly enhance DA by blocking GABAergic interneurons in the VTA,

disinhibiting them, and triggering mu opioid receptors (MOR) in NAc neurons[16]. Target receptors of opiatesand its mechanism of action are given in table 1.

Table 1: Shows pharmacological targets of opiates.

	Target receptors	Mechanism of action
OPIATES	μ (mu) (MOR)	Opioids such as morphine, heroin, and fentanyl are MOR agonists[17].Opioid activation of MOR in the VTA promotes striatal dopamine release.
	δ (delta) (DOR)	
	Ƙ (kappa) (KOR)	

Management of substance abuse in Unani Medicine

The treatment of drug misuse is critical for reducing its health and societal repercussions. Drug addiction management requires a multidisciplinary approach, which includes not just managing withdrawal symptoms but also addressing the psychosocial issues that contribute to drug dependence. There are several therapy strategies for substance use problems. Because patients with substance use disorders who are receiving standard pharmaceutical therapies may still relapse, incorporating alternative treatments such as medicinal plants into addiction treatment may have positive results[7].The Unani System of Medicine offers enormous potential in the areas of de-addiction and rehabilitation. The System not only manages withdrawals but also promotes psychosocial behavior/ailments[18]. Unani medicine has a large number of single and compound medications that have been successfully utilized to treat these symptoms.The Unani system of medicine has a unique idea of *Ilāj Nafsānī* (psychiatric treatment). This treatment comprises treating psychiatric problems with medications or modifying the Six Essential Factors of Life (*Asbāb Sitta Zarūriya*). Following these factors can help to prevent substance misuse[19]. *Ilāj Ruhānī* (Spiritual Treatment) can treat psychiatric and drug abuse illnesses, including meditation. This system comprises traditional therapeutic and interventional techniques such as *Ilāj bil Tadbīr* (Regimen Therapy), Consultation, and Meditation to diagnose and detoxify from drug dependence[20].

The Unani System offers *Musakkināt* (Calming Drugs) to help treat drug abuse. These are medications that relax the nervous system but do not stimulate it in any way and do not promote dependence. *Mufarrihāt* (exhilirant drugs) such as *ābresham* (Silk Cocoon), *ilāichī* (*Elettaria cardamomum* (Linn.) Maton), *balango* (*Lallemantia royleana* Benth.), *jāwetrī* (*Myristica fragrans* Houtt.), *gul-i-gaozabān* (Onosma bracteatum), *gul-i-Surkh* (*Rosa damascena* Mill.), are among the exhilirant drugs that can help elevate mood. Unani compound medications like *Ma'jūn Najā*, *Ma'jūn Nasyān*, and *Ma'jūn KhadrJadīd* can assist manage substance dependency. The Unani traditional book, *Qarābādīn-i-Azam*, expressly

mentions *Ma'jūn Kuchla* as the ideal formulation for treating and managing opioid addiction[21,22,23]. *Habb-i-shifa*, a pharmacopoeial formulation from *Ilāj-ul-Amrāz*, contains *Dhatūra* (*Datura stramonium* Linn.), *Zanjabīl* (*Zingiber officinale* Roscoe), *Rewand chīnī* (*Rheum officinale* Baill.), and *Samagh arabī* (*Acacia arabica*) for opioid de-addiction[23]. Several animal studies have looked into the efficacy of *Habb-i-shifa* in treating withdrawal symptoms such as muscle aches, colic pain, rapid sedation, anxiety and irritability reduction, and depressive symptoms.

Hence, the purpose of this review paper is to highlight the de-addiction capabilities of *Habb-i-shifa* in the Unani system of medicine, as well as to identify its mechanism of action inde-addiction based on experimental research.

METHODOLOGY

Various classical books from the accessible literature on drug de-addiction in Unani medicine, Indexed journals were surveyed for relevant content using keywords such as "opioid addiction" and "Unani medicine and de-addiction," and the results were filtered for this review.

HABB-I-SHIFA

Habb-i-shifa is a pharmacopeial Unani formulation mentioned in various Unani classical texts such as *Al-qarābādīn*, *Bayāz kabīr*, National formulary of Unani Medicine.

Af'āl (Actions)

Dāfi'-i-tapp(antipyretic), *Dāfi'-i-tashannuj*(anticonvulsant)[24],

Iste'mālāt (Therapeutic uses)

It is quite beneficialin *Afiyūn ki lat* (de-addiction of opium), *Hummā* (fever), *tashannuj rewī*, *zīq-un nafs* (asthma), *sudā* (headache)[24,25].

Miqdār khurāk (dosage)[26]

1-2 pills per day.

Compositionof *Habb-i-shifa*

The individual ingredients of *Habb-i-shifa*with their botanical names and quantities to be taken in a formulation are given in table 2[26].

Table 2: Shows composition of *Habb-i-shifa.*

Ingredient	Botanical name	Quantity
Dhatūra	*Datura stramonium* Linn.	36 g
Zanjabīl	*Zingiber officinale* Roscoe	12 g
Rewand chīnī	*Rheum emodii*	24 g
Samagh arabī	*Acacia arabica*	12 g

Description of ingredients of *Habb-i-shifa* in Unani Medicine:

Pharmacological actions and therapeutic uses of individual ingredients of *Habb-i-shifa*mentioned in Unani classical texts is given in table 3[27,28,29,30].

Table 3: Shows individual ingredients of *Habb-i-shifa* with their pharmacological actions and therapeutic uses.

Ingredient	Part used	Pharmacological action	Therapeutic uses
Dhatūra	Seeds	Nerve sedative, cerebral depressant, sedative, dessicative, Antidote	Opium de-addiction, headache, epilepsy, palpitations
Zanjabīl	Rhizome	Digestive, stomachic, deobstruent, aphrodisiac, carminative	Fever and chills,diuretic, cough,asthma, haemorrhoids, Withdrawal-induced nausea, diarrhoea and muscle pain
Rewand chīnī	Root	Purgative, brain purgative, carminative, analgesic deobstruent, anti-inflammatory	Indigestion, antidote for scorpion bite, wound healing, fever, cough, ascites, dysmennorrhoea
Samagh arabī	Gum	Astringent, dessicative, Emolient, Stomachic, intestinal tonic	Drug De-addiction, Conjunctivitis, Cough, Diarrhoea, headache, Sore throat

MECHANISM OF ACTION OF *HABB-I-SHIFA*IN DE-ADDICTION

Mechanism of de addiction of different ingredients of *Habb-i-shifa*is mentioned in table 4.

Table 4: Shows mechanism of action of individual ingredients in de-addiction.

	Mechanism of action
Dhatūra	GABAA receptors[31], serotonergic system[32], increased BDNF expression and improved neuro-system function[33], modulatory effects on monoaminergic and cholinergic neurotransmission systems[34], and modifies purinergic enzyme activity[35].
Zanjabīl	Potential MAO inhibitory activity[36]and anti-inflammatory activity through the PI3K-Akt-mediated NF-κB pathway. Activates the MEK/ERK signal pathway, which increases the production of DA, 5-HT, and NE[37]. Boosts GR and BDNF levels in the hippocampus[38].
Rewand chīnī	Reduces the expression of TNF-α, IL-6, and IL-β[37]. Increases the quantities of 5-HT and DA; boosts the expressions of BDNF, NGF, TrkB, and TrkA in the hippocampus[39]; induces neuropeptide Y (NPY) expression[40]

EXPERIMENTAL STUDIES ON *HABB-I-SHIFA*FOR OPIATE DE-ADDICTION ACTIVITY

The effectiveness of *Habb-i-shifa* in controlling withdrawal symptoms such as muscle aches, colic pain, rapid sedation, reducing anxiety and anger, and relieving depressive symptoms has been evaluated in various animal studies as follows

1. One study conducted out by M. Mujassam, Rafiuddin Khan, Ghulamuddin Sofi and Mustafa Shakirin 2014 in NIUM, Bangalore,was designed to evaluate the attenuating effect of 50% alcoholic extract of *Habb-i-shifa* in morphine dependent Wistar rats. From this study it was inferred that the test drug attenuated to a significant degree the behavioural manifestations of morphine withdrawal syndrome and validated the claims of Unani physicians regarding the clinical use of *Habb-i-shifa* in de-addiction of opium.
2. Another study carried out by Mujassam M, Sofi G, Shabir P and Wasim A in 2020was proposed to evaluate the effects of *Habb-i-shifa* on Naloxone precipitated morphine withdrawal symptoms in swiss mice. *Habb-i-shifa* produced significant degree of effect on morphine withdrawal syndrome and thus validated the Unani medicine claim that *Habb-i-shifa* is an important drug to be useful in the management of opioid withdrawal.

CONCLUSION

In the light of above information from the Classical text of Unani Medicine, it may be concluded that this System has got a tremendous potential in combating the problem of opioid abuse. There are many single and compound Formulations written in Classical text that can help in managing the problems related to substance abuse and withdrawal symptoms. Of these, *Habb-i-shifa* has been clinically validated and scientifically proven and there is a need of further validation studies so that it benefits the suffering population.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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