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HERBAL DRUGS FOR THE TREATMENT OF OPIOID WITHDRAWAL SYNDROME : A MINI REVIEW

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Abstract

Addiction to opioid drugs is the extensive medical and social burden of human life. Chronic usage of morphine in the severe pain has also been associated with its major drawback for development of dependence and tolerance. In different brain regions, there are various receptors which play important role in opioid withdrawal syndrome. The herbal drugs; like *Nigella sativa, Withania somnifera, Aloe vera, Matricaria recutita*, venlafaxine, curucumin play vital role to treat the abstinence syndrome. Most of the above mentioned drugs are related with some adverse effects. So there is need to develop some novel agents targeting the various mechanism underlying the opioid withdrawal, thereby providing significant relief from opioid withdrawal syndrome. In this review, we discussed the usefulness and limitations of various drug treatments for opioid withdrawal syndrome.

***Keywords*:** Opioids, Withdrawal syndrome, Drug addiction, Tolerance, Dependence, *Nigella sativa*, Curucumin, *Withania somnifera*

Introduction

Drug addiction is a stage in which a subject feels to administer frequently a psychoactive substance. This rehearse substance use become visible to be a learned behaviour that is enlarged both by the euphoria effects of the substance and by the negative effects of opioid substance withdrawal (Clausen *et al.,* 2009). Physical and psychological dependence materialize which result from neuronal adaptation in the presence of the any opioid drug in different brain. The brain regions which are involved in opioid withdrawal are PAG (periaqueductal grey), VTA (ventral tegmental area), NAcc (nucleus accumbens) and dorsal raphe. Common neuronal pathways are mediated by the effects of psychological dependence that results behavioural reinforcement of opioid drug use (Eddy *et al.,* 1965). On the contrary, physical dependence is due to the continued presence of a drug in the specific areas of the brain to the continued presence of a drug. It has a strong relation with both the drug tolerance and development of specific drug withdrawal syndrome (Himmelsbach, 1942). Addiction is related with a chronic level of drug dependence followed by withdrawal syndrome (Jaffe, 1990). Morphine and heroin are the most commonly abused drugs from which (O'Brien, 1996) morphine is a highly efficacious opioid analgesic that is widely used for acute and chronic pain control and its chronic use permits the withdrawal syndrome (Anthony and Helzer, 1995). which reduces the therapeutic efficacy of these drugs. (Kosten and George, 2002). Opiate drugs like heroin, morphine showed their effects by binding to three specific opioid receptors (μ, γ, and κ). The specific μ opioid receptor (MOR)is responsible for the rewarding effects of heroin and morphine. The most prominent neuroadaptive changes during morphine induced dependence include desensitization of MORs and upregulation of the cAMP pathway. The MAPK (mitogen activated protein kinase) pathway and Ca^{2+} signaling are also affected during morphine dependence. The primary consequence of morphine withdrawal is 'superactivation' of adenylyl cyclase (AC) and a subsequent overproduction of its downstream signaling molecule, cAMP. Other cAMP actions during withdrawal include PKA-mediated enhanced GABAergic synaptic transmission in areas such as periaqueductal grey (PAG), Ventral Tegmental area (VTA), Nucleus Accumbens (NAcc.) and dorsal raphe (Bailey and Connor 2005). Extensive research is going on for the development of new non-addicting opioids drugs or agents that can prevent or reverse the addiction processes like methadone, it is a long-acting opiate drug, used for detoxification from opiate medications and in reducing symptoms of opioid withdrawal for intravenous opiate users but if the subject will use this drug as longer can also cause dependence of this drug specifically. Secondly clonidine also reduce the symptoms of opiate withdrawal and various drugs which are discussed below. However, but none of the options is available to manage the condition of abstinence syndrome for opioids. (Law *et al.,* 2000). So there should be new ways to prevent addiction and withdrawal symptoms would be of great clinical benefit. Currently, attention has focused on a number of drugs which should be used for the management of morphine withdrawal and positively possessing the above-mentioned pharmacological profile (Ward *et al.,* 2011; Williams *et al.,* 2001).

Herbs as Drugs

(i) *Nigella sativa*

Nigella sativa, a non-opiate drug, belonging to the family Ranulaceae which is free from euphoria effects and can treat the opioid withdrawal symptoms effectually. (Nutt 1996) Its seeds are used as condiment and herbs have various uses. It is also called as '*kalonji*' in subconyinent and is known as '*Habatul Saud*' in Arabic name. (Nandakarni, 1976) which is known as "Black Cumin". *Nigella sativa* are calcium channel blockers, blocking the action potential in both neuronal and peripheral tissues. The target of the current study was to check the effects of *Nigella sativa* in morphine withdrawal syndrome. In this study, the selected patients

(preferably men) with morphine/heroin abstinence syndrome, dose of *Nigella sativa* 50 mg were given by oral route. The withdrawal subjects which acquired single blind placebo capsule by oral route which contain the ferrous sulphate during 1st day and 2ndday. After the drug administration, the observer observed the positive signs and negative signs of opioid abstinence syndrome during the prior 24 hours, After giving the treatment, group who acquired 500 mg of *Nigella sativa* on third day of treatment (treatment day-1) called single blind capsule. Moving to the 1st infusion of drug, those subjects who give the affirmitive response to the drug towards morphine symptoms of withdrawal and without showing any side effects were given the treatment up to day twelve. (treatment day-10). The patients who are suffering from anxiety were given the diazepam (5 mg) for their treatment. During the previous 24 hours, the withdrawal signs and symptoms covered the ratings. On day twelve their respective treatment of admission of urine specimens showing positive results in all the patients but showed minor adverse effects when tested with dipstick patients of *Nigella sativa* (500 mg) treatment in frontline opiates. The researcher concluded that placebo on day-1 and day -2 admission of drug, the first three days administer of drug, the opiate withdrawal syndrome only observe and confirm. *Nigella sativa* was administered 500 mg thrice a day in daily routine, Pretreatment of *Nigella sativa* 500 mg decreased the symptoms of withdrawal on third day rating rate. It has been also revealed that *Nigella Sativa* seeds of volatile oil also terminated the spontaneous mobility of animal (rat), the contraction of uterine smooth muscles of guinea pig induced by oxytocin stimulation in both the studies of *in vitro* and *in vivo* (Aqel and Shaheen, 1996). It also shows its anti-inflammatory activity also (Houghton *et al.,* 1995) and used as a contraceptive (Keshri *et al.,* 1995).

(ii) *Withania somnifera*

It is also called as Ashwaganda, belonging to the family solanaceae, is an adapotgen tonic herb, which is also called as a nervine restorative. It is also used in the treatment of benzodiazepine withdrawal syndrome, which role as an GABA receptors agonist. (Rasmussen and Phil, 1997). It show its effect in the over activity of nervous system and anxiety associated with withdrawal syndrome. (Winston *et al.,* 2007). Herbs such as *Pimpinella anisum* reduces the sweet based cravings by naturally increasing the blood sugar level which are useful on a more physiological level (O' Brien and Tom, 2012). Rasmussen, a Herbalist recommends that higher doses of herbs in the early phases of abstinence syndrome built up chronic drug use of any opioid drug due to the down regulation of receptors in the body (1997:3). Opioid abstinence is related with structural changes of specific dopamine neurons in the VTA (ventral tegmental area) and with decreased density of spine. In a number of experimental models of neurological disorders. Methanolic extract of *Withania somnifera* and with an olides (constituents) have both synaptic reconstruction and neuritic regeneration properties. The researcher also revealed that when the *Withania somnifera* extract is administered, the morphine withdrawal induced spine is reduced in the nucleus accumbens (NAc). In the present study, the treatment group of animals (rats) were severely received *Withania somnifera* along with the opioid drug and the control group of animals saline was given and their brain regions were kept in Golgi-Cox stain for study of confocal microscopic examination upon spontaneous and precipitated opioid withdrawal syndrome model (1st and 3rd day). In a separate group of animals, *Withania somnifera* extract was administered during the three days of spontaneous withdrawal syndrome. From this group, it was found that extract of *Withania somnifera* decreased the severity of abstinence syndrome in rich morphine administration not in withdrawal syndrome. On this treatment, the researcher revealed that in the part of the brain nucleus accumbens, the decreased spine density is fully prevented in both spontaneous and precipitated morphine withdrawal syndrome. The researcher also mentioned that the results shows that morphological changes which is induced by opioid withdrawal providing potentially effects when pretreated with the extract of *Withania somnifera*. (Kasture *et al.,* 2009)

(iii) *Aloe Vera*

A cactus-like enduring plant *Aloe vera* belongs to the family Liliaceae. It grows in both hot and dry climates of tropical part of the world (Asadi-Shahmirzadi *et al.,* 2012). The component of *Aloe vera* contain acemannan which is a polysaccharide and has an anti-inflammatory effect on oral aphthous ulceration (Hajhashemi *et al.,* 2012; Bhalang *et al.,* 2013; Sudarshan *et al.,* 2012; Devaraj *et al.,* 2013) . It also supports to treat the severe and prolonged wounds with the use of Aloe vera dressings (Dat *et al.,* 2012). Shin *et al.* mentioned that the complex extract of *Aloe* could improve syndromes related to diabetes and insulin resistance in mice fed with a extreme fat diet (Shin *et al.,* 2012). Experiments with *Aloe vera* leaf showed that it has protective antihyperglycemic effect and gave a positive results towards the hyperlipidemic diabetes type 2 patients. (Huseini *et al.,* 2012). Researchers have clearly shown that various medicinal herbal extracts suppress opioid withdrawal in laboratory animals (Alemy *et al.,* 2012). Hajhashemi *et al.* mentioned that *Aloe littoralis* have apparent anti-inflammatory and wound-healing effects on animals (Hajhashemi *et al.,* 2012). In addition, *Aloe vera* dose of 400 and 200 mg/kg, (p.o) significantly attenuates the 2nd stage pain of formalin induced. (Rathor *et al.,* 2012). Moreover, it is also effective as a ointment which is effectively reduces the postoperative pains after hemorrhoidectomy when applied on the surgical sites (Eshghi *et al.,* 2010). However, *Aloe vera* has also positively anti-PLA2 antibodies and anti-inflammatory effects on animals (Kammoun *et al.,* 2011; Rishi *et al.,* 2008). Since *Aloe vera* has both nociceptive and anti-inflammatory effects. Hence the researcher evaluated the response of aqueous extract of *Aloe vera* on opioid dependent female rats in the model of opioid withdrawal syndrome.

In this, the researcher evaluated the response of extract *Aloe vera* opioid dependent female rats in the model of opioid abstinence syndrome. The study was done on 40 adult Wistar albino female rats. During the first week of experiment all animals were kept with standard rodents. After the fifth day completion of habituation of morphine twice a day, the rats were kept morphine-dependent (Houshyar *et al.,* 2003). All the animals were separated randomly into 5 groups (i, ii, iii, iv and v, n = 8) from which group (i) receive none during the trial days i.e. control group, and the groups (ii, iii, iv and v) received extract of *Aloe vera* at doses of 5, 10, 20 and 40 mg/kg for a period of thrice a day for a week, respectively. The symptoms of opioid withdrawal like floppy eyelids, stability, stool form and agitataion were observed thrice times daily. The conclusion of the present

study revealed that the groups who received extract of *Aloe vera* of dose 5mg/kg and 10 mg/kg gave positive response as contrast with the other groups. The equilibrium in the group is achieved in 10 mg/kg of *Aloe vera* aqueous extract daily significantly decreased as comparison with the other groups; however, this parameter in the group received 40 mg/kg of drug gave positively increased response as contrast with the vehicle group. In addition, the results of the above study observed that the withdrawal symptom floppy eyelids in the 10 mg/kg of *Aloe vera* aqueous extract group was positively decreased as contrast to the control group, but this symptom in the group of 40 mg/kg, the drug was significantly increased as comparison to the control group. The withdrawal symptom agitation is reduced in those groups who received 10 mg/kg *Aloe vera* (aq) significantly lower as compared with the vehicle group, but the group who received the dose of 40 mg/kg, the withdrawal symptoms positively increased as contrast with vehicle groups. Similarly, type of stool show no response any in the groups. The conclusion of the current study showed that the morphine withdrawal syndrome such as floppy eyelids, agitation, imbalance, and in morphine-dependent group was lower as compared with the vehicle group. However, these observations in morphine-dependent group gave higher response as comparison to the vehicle group in the period of treatment. In addition, the average weight in groups ii and iii was higher when compared to the saline group. The stool form show none positive differences in the groups. From the above research, the researcher concluded that extract of *Aloe vera* had unrelated effects in morphine withdrawal syndrome in morphine-dependent female animals (rats). So more knowledge are required to search out the true mechanism of these pharmacological effects and also the active ingredients which are engaged for these effects (Mohammad *et al.,* 2014)

(iv) *Matricaria recutita*

Matricaria recutita (*M. recutita*) (Chamomile) associated to the family asteraceae, is broadly used for its potential clinical and therapic benefits. Clinical benefits of *M. recutita* are anti-inflammatory, anti-ulcer, anti-bacterial, anti-fungal and anti-viral anxiolytic, spasmolytic, sedative, anti-allergic effect. Potentially active chemical components present in *M. recutita* are terpenoids, coumarins flavonoids, and Spiro ethers (Gardiner and Chamomile, 1999; Nmecz, 2000). Flavonoids of *M. recutita* have special place in different studies (Gardiner and Chamomile, 1999; Nmecz, 2000; Avallone *et al.,* 2000). It has contains several benzodiazepine like ligand and has inhibitory factors that affects the progression of morphine dependence. The researcher suggested that the inhibitory property of *M. recutita* on morphine withdrawal syndrome express is related to the activity of benzodiazepine (Avallone *et al.,* 1996; Bateson, 2004; Capasso *et al.,* 1998; Gomaa *et al.,* 2003). Therefore, the effect of *M. recutita* on opioid withdrawal signs as a result of naloxone along with administration of effective factors on benzodiazepine receptors has been investigated *M. recutita* (25mg/kg) decreased significantly the sign of climbing in morphine withdrawal rats in comparisons to control group ($p<0.001$), but it does not change other signs significantly.

The researcher revealed that *M. recutita* decreases the dependence andmorphine withdrawal syndrome which express bybenzodiazepine receptors. It has been shown that benzodiazepine bind to $GABA_A$ receptors subunitsin neuronal-membrane of CNS. Therefore, it has been revealed that the sedative effect of *M. recutita* on opioid syndrome is in relation with benzodiazepine like compounds that act by $GABA_A$ receptors. The researcher concluded activation of ligand gated ion channel in which the benzodiazepine receptor is activated by the GABA and increase the GABA effect of benzodiazepine component on channel, therefore normally hyperpolarization of neurons results in decreased the action potential firing and thereby a decreased the neuronal response and hence result in a sedative effect (Gardiner and Chamomile, 1999; Avallone *et al.,* 1996; Bateson, 2004; Gomaa *et al.,* 2003; Berreler *et al.,* 2004).

Phytochemical Constituents as Drugs

(i) Curucumin

Curcumin is a pigment which is yellow in colour and is one of the major constituents of turmeric rhizomes. Turmeric (*Curcuma longa*) relate to the zingiberaceae ginger family, is a rhizomatous herbaceous dahlia plant having many medicinal uses. The fraction of curucumin has important therapeutic and medicinal properties. Rhizomes extracts of *C. longa* is a major constituent, which has been effectively served in the remedy of pain, stress, depression, drug dependency, and related disorders (Sharma *et al.,* 2006; Sharma *et al.,* 2007; Xia *et al.,* 2007). It also contains immunomodulatory, anti-inflammatory, antioxidant, anticancer, and neuroprotective properties (Durgaprasad *et al.,* 2005; Motterlini *et al.,* 2000; Varalakshmi *et al.,* 2008; Sharma *et al.,* 2001; Xu *et al.,* 2007) and antinociceptive effect also. Previous studies indicated that naloxone which is opioid receptor antagonist decreases the curcumin antinociceptive activity in acetic acid caused visceral pain or the pain occurred in opioid withdrawal syndrome. In this study, Morphine dependence was given by the injection of opioid (morphine) (20-45 mg/kg) in 5 groups of rats. Morphine was injected by subcutaneously with an increasing dosage manner for 6 days. On the 13th day, all animals in each group were induced with naloxone 3 mg/kg, and behavioral studies were recorded by a camera of each animal. Recorded behaviors are jumping, headshake, wet dog shake, forepaw tremor. Experimental studies have shown that some species of Salvia have effective against opioid drug addiction (Yeh *et al.,* 2002; Motaghinejad *et al.,* 2014). Example, *S. leriifolia* Benth. and *S. limbata* C.A. Mey. attenuate morphine dependence in animal (Sharma *et al.,* 2007; Xia *et al.,* 2007). *Salvia officinalis* L. (SO) an aromatic plant has various pharmacological effects on CNS like neuroprotective. (Yeh *et al.,* 2002), antinociception (Motterlini *et al.,* 2000) antioxidant (Durgaprasad *et al.,* 2005) and memory enhancing (Varalakshmi *et al.,* 2008) effects. It has also been proven that some flavones present in the extract of SO can activate chloride channels of receptor present in the GABA. (Sharma *et al.,* 2001) which may be a mechanism for the anti addiction action of SO. Additionally, have the potent anti-inflammatory and antioxidant effects (Durgaprasad *et al.,* 2005; Xu *et al.,* 2007; Ohn *et al.,* 2009) of SO which could also be responsible to treat the addiction action of SO. The above described results of SO may involve an opioid mechanism. (Motterlini *et al.,* 2000; Tajik *et al.,* 2007). Therefore, the researcher examined that the protective effects of different doses of SO hydro alcoholic extract (400, 600 and 800 mg/kg, i.g.) on morphine-caused dependence in rats. The analgesic effects of SO at different doses and included some measures for non-selective sedative effects of

SO to suggest a behavioral mechanism through which SO may act to counter the progression of morphine dependence. To induce analgesic sufferance, morphine was administered two times daily i.e 8:00 am and 6 pm at a dose of 10 mg/kg for period of 7 days. For determination of SO effect on the progression of opioid tolerance, SO (400, 600 and 800 mg/kg, i.g.) or 3% Tween 80 was given 30 min prior to individual s.c. injection of opioid. Tail Flick (TF) intervals were also calculated on days 1, 3, 5 and 7 during treatment (Mittal *et al.,* 2009) 30 min after morphine injection. The researcher also determined the effects of SO extract alone in TF test to check the analgesic effect of SO. TF latencies were measured 60 min after the extract administration of SO. To check the opioid withdrawal symptoms, animals (rats) were administered subcutaneously route with morphine, two times daily, for 7 days. 1st and 2nd, the dose of morphine was 2.5 mg/kg; to reach a dose of total 40 mg/kg on 6th, 2.5 mg/kg dose was doubled everyday. After this, on 7th day the rats administered the final dose of morphine i.e. 50 mg/kg. SO (400, 600 and 800 mg/kg, i.g.) or 3% Tween 80 was given 30 minute before the administration of opioid to discover the effect of SO on the progression of opioid withdrawal. On the 7th day, for the model of precipitation of opioid withdrawal syndrome, the dose of naloxone i.e. 3 mg/kg, s.c was administered 5h after the last injection of morphine. Without delay, after opioid antagonist i.e naloxone injection, rats were kept in a Plexiglas observation chamber having dimensions 30×30×30 and the withdrawal symptoms were noted for 30 minutes after the administration of naloxone: the abstienance symptoms are weight loss, jumping, rearing, teeth chattering, standing, sniffing, wet dog shakes and face grooming. An independent observer was required, who was unforeseen of the treatment received, and will evaluate the response of individual animal of each group. (Gupta *et al.,* 2009). The SO effect on the progression of opioid withdrawal was measured the %age of loss weight before and after naloxone administration in both the treated and untreated opioid withdrawal groups. Administration of naloxone in the opioid withdrawal group caused the loss of weight. The 400 mg/kg dose of SO had no weight loss in the naloxone precipitated animal model, higher dose of SO (600 mg/kg and 800 mg/kg) showed the attenuated weight loss in opioid dependent animals as comparison to untreated opioid dependent groups. The researcher measured the results of SO medication on the count of jumping behaviour in the opioid-relaint rats and examined that after the naloxone injection the count of jumps increased in the opioid dependent rats and the administration of SO at different doses (400, 600 and 800 mg/kg) in the opioid-reliant rats significantly decreased the count of naloxone-precipitated jumps as comparison of the opioid-dependent batch. It was showed that the difference of doses did not showed to suppress the jumps count. It has been shown that SO suppress the occurrences of teeth chattering in different animals of groups at different doses. The higher doses (600 and 800 mg/kg) of the SO significantly attenuated number of teeth chattering events in opioid-dependent animals when compared to untreated opioid-dependent rats. The dosage of 400 mg/kg SO did not decrease significantly in the number of teeth chattering syndrome in opioid reliant animals. Administer of naloxone by using naloxone precipitation model, a cluster of other withdrawal symptoms are wet dog shakes, face grooming, sniffing, paw tremor, standing, and rearing in morphine-reliant rodents, SO 400 mg/kg did not change any of these abstinence signs in morphine-dependent animals when compared to vehicle treated morphine-dependent group. However, the researcher summarized that higher doses of the SO extract (600 and 800 mg/kg) attenuated the signs of morphine withdrawal symptoms. For example, both SO 600 and 800 mg/kg decreased the numbers of wet dog shakes and sniffing. However, SO 800 mg/kg, but not 600 mg/kg, reduced paw tremor standing, face grooming and rearing in SO 800 mg/kg treated-morphine dependent rats. The researcher concluded from the above data that the findings may have clinical relevance because they suggest that the combination of SO with morphine may attenuates the side-effects of chronic any opioid use drug use but the strategy of combination therapy could also lead to decreased morphine dosing without changing its efficacy.

Conclusion

Opioid addiction is a social problem which is complicated by the phenomenon of tolerance followed by dependence. Contrast with different drugs of misuse morphine dependent advantage from a broader range of present pharmacological tools for treatment. Beside this, the majority subjects (one million) opioid misusers and two to three million prescription morphine misusers are not taking treatment. From the above review, it is concluded that the most successful treatment drugs like *Nigella sativa*, clonidine, lofexidine, curucumin, memantine, *Withania somnifera*, *Aloe vera*, *Matricaria recutita* and venlafaxine but a variety of obstacles, including side effects, slow action and availability combine to diminish their use. In addition to dealing with the barriers above, there is need a drug which have less side effects, should be easily available and has good pharmacological effect so has to decrease opioid withdrawal syndrome.

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