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Research Article

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Nigella sativa Effects on Neurotransmitter Systems: Potential Treatment for Drug Tolerance and Dependence

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ABSTRACT

Drug dependence and tolerance is becoming an enormous health problem worldwide and significantly affect the society. Although currently there are approved drugs used for the treatment of drug dependence and tolerance, these compounds also pose with some notable adverse effects and issues, i.e. drug-dependency and withdrawal problems. Therefore, there are emerging needs for a naturally existing substance such as Nigella Sativa (N. sativa) which can be used as an alternative treatment to treat addiction illness, which may present as natural resources. N. sativa is one of these natural substances that gaind its popularity due to its unique chemical properties. In Islamic literature, N. sativa was mentioned as one of the effective forms of a therapeutic agent and healing medicine. It has promising effects as an anticancer, antioxidant, anti-inflammatory and many other benefits. In addition, several pharmacological research also has been done to investigate the effects of N. sativa bioactive compounds on drug dependence and tolerance. Hence, this review focuses on the effects of N. sativa bioactive compounds on the neurotransmitter systems, and its role in reducing drug dependence and tolerance.

Key words: *Nigella Sativa, Bioactive Compounds, Neurotransmitters, Drug Tolerance.*

INTRODUCTION

Drug dependence and tolerance is becoming an enormous mental health problem and physical effects worldwide and significantly affect the society. Drug dependence refers to physical dependence in which the body adapts to the chronic used of drugs. An individual who develops dependence is subjected to withdrawal symptoms, which include fatigue, shaking, and nausea on cessation of the drug intake. Meanwhile, drug tolerance refers to a physiological state where a higher dose of the drug is needed in order to achieve the original effect after repeated use of the drug [1]. Repeated administration of the illicit drug may cause the development of drug dependence and tolerance [2].

In this current era, natural substances which produce fewer side effects are being explored for the treatment of various diseases including drug addiction. One of these natural substances is N. sativa. Studies on N. Sativa proposed its antioxidant, anti-inflammatory, anti-cancer, and neuroprotective agent. Besides that, the couple of studies also revealed that N. sativa has the potential to alter the neurotransmitter systems mainly the dopaminergic,

serotonergic and gamma-aminobutyric acid (GABA) systems which is one of its potential mechanisms to alleviate drug dependence and tolerance [3]

Nigella sativa properties and its therapeutic remedies

N. sativa is one of the Ranunculaceae family botanical plants. It normally grows in the Middle East, Western Asia and Eastern Europe [4]. The plant grows up to 90 cm tall. It produces flowers of various colours yearly. The seed of N. sativa is known as Black Seed. It is a rich source of active ingredients such as fixed and essential (volatile) oil, carbohydrates, vitamins, saponins, organic acids, proteins and amino acids [5]. For centuries, Nigella sativa seed and its oil have been widely used to treat various health problems. It is also one of the effective natural drugs which is used in some of the regions in India such as Unani and Ayurveda [6].

For many years, N. sativa has been used as therapeutic agents to treat many ailments due to its numerous properties. It is explored for its biological activities, bioactive compounds, and restorative potentials in order to further identify its benefits for the development of an alternative treatment. Many studies reported that N. sativa contains a lot of bioactive compounds. The main bioactive compound is thymoquinone (TQ) which constitutes up to 48% of the compounds. Besides, thymohydroquinone, dithymoquinone, and p-cymene are also reported to contain up to 15% of the bioactive compounds. Other minor compounds include carvacrol (up to 12%) 4-terpineol, t-anethol, sesquiterpenelongifolene (less than 10%), thymol and others [7]. Other studies also indicated that N. Sativa seeds contain carbohydrates, protein, fat and crude fiber [8] as well as vitamin A, mineral and fatty oil rich in unsaturated fats [9].

Since TQ is the major bioactive compound of N. sativa, it holds a great potential as a therapeutic medical plant to treat cancer, oxidative stress and inflammation. The N. sativa oil can also act as an anti-schistosomiasis agent against liver damage caused by Schistosoma mansoni [10]. Furthermore, methanol extraction of N. sativa has an ability to prevent fungal activity while aqueous extraction can induce analgesic activity [11].

Traditionally, N. sativa is used as an effective therapeutic agent for various disorders and diseases such as asthma, headache, bronchitis, fever, and rheumatism [12]. It is also studied for its preventive effects against neurotoxicity and for its neuroprotective effects against neurodegenerative diseases such as Alzheimer disease and Parkinson disease [13]. Moreover, a recent study discovered that N. sativa has the potential effect to reduce drug dependence and tolerance [14]. All these studies strongly suggest that N. sativa is among the most effective herbal medicines that have been proven experimentally.

Effects of n. Sativa in-vivo and in-vitro studies

Studies by Abdel Zaher et al., (2011) discovered that N. sativa has an important role in reducing drug dependence and tolerance in-vivo. For instance, previous studies on N. sativa oil (NSO) proved its great therapeutic potential of NSO in inhibiting the development of tramadol (an opioid drug) dependence and tolerance in mice. After repeated administration of NSO along with tramadol, NSO demonstrated the ability to prevent the overproduction of nitric oxide and oxidative stress induced by tramadol and reduced the development of glutathione and glutathione peroxidase in the brain [14].

Hosseinzadeh et al., (2016) reported that a single dose or repeated administrations of TQ attenuates dependence and tolerance induced by morphine in mice. The tolerance and withdrawal symptoms were measured using hot-plate test. Tolerance and withdrawal to morphine were indicated by the number of jumps by morphine-dependent mice and hot plate test. The result of this study showed that TQ significantly reduced the number of jumps by the mice and the hot plate test result demonstrated that TQ significantly alleviates the development of tolerance to the analgesic effect of morphine [15].

The effects of N. Sativa in reducing drug dependence and tolerance was also studied at the cellular level. A recent study proved that TQ has the potential to increase the expression of the mu-opioid receptor protein in U-87 opioid receptor-expressing cell line after chronic morphine treatment. From this study, it can be concluded that TQ has a great potential to be used as a supplement to reduce drug dependence and tolerance by increasing Mu opioid receptor (MOR) protein concentration [16].

Nigella sativa effects on neurotransmitter systems

Drug administration, especially the psycho-stimulant group of drug may give an impact to the neurotransmitter systems. Neurotransmitters are the chemical messengers released by neurons that play an important role to carry out body functions such as working memory, motivational behaviour, and regulation of movement and mood [17].

Most of the psychostimulant drugs disrupt the activity of the neurotransmitters within the synapses of the brain. Besides that, different psychostimulant drugs have different effects on different neurotransmitters [18]. For example,

a drug such as amphetamine (AT) causes an increase in dopamine (DA) level. AT reverses the reuptake of DA by binding to the dopamine transporter (DAT) at the presynaptic terminal, causing free DA to be released out of the nerve terminal. Since AT has a similar chemical structure to DA, it can bind to the DAT firmly [19].

Other drugs such as opioid drugs (heroin and morphine) bind to endorphin receptors in the brain that give a response to painful stimuli. Vanegas, Vazquez, and Tortorici (2010) found that the ability to tolerate pain reduces from time to time in chronic opioid users as these receptors are activated repeatedly and this leads to tolerance to the drug [20].

To date, several studies have been carried out with regards to the neurotransmitter systems in the treatment of drug dependence and tolerance. Other study reported that N. sativa possesses the ability to interact with neurotransmitters such as dopamine, serotonin, GABA, and acetylcholine and give a positive effect by reducing drug tolerance [3].

In 2013, El-shamy reported that TQ has the potential to reduce monoamine neurotransmitters (dopamine, serotonin, and norepinephrine) in the cortex and hippocampus of rats' brains after being treated with nicotine. Administration of nicotine causes an elevation in the concentration of monoamine neurotransmitters. Nicotine promotes the release of monoamine neurotransmitters by activating tyrosine hydroxylase and monoamine biosynthetic enzyme and also by binding to the nicotinic receptors. The changes in neurotransmitter level after administration of TQ are proven to be approximately similar with the control-like values. Hence, they concluded that TQ may play a role in assisting smokers to stop smoking by relieving the withdrawal symptoms of nicotine [21].

It was studied that TQ acts as a positive modulator of GABA in the GABAergic system to reduce alcohol dependence and tolerance. GABA promotes the action of TQ pertaining to the motive circuitry of the limbic component of the basal ganglia. Moreover, TQ has a great potential to reduce behavioural locomotor sensitization induced by alcohol [22].

It was reported that natural compounds having antioxidant properties can give beneficial effects in the treatment of drug dependence and tolerance. For instance, the effect of TQ in animal models of schizophrenia was reported by Rashid Ali Khan and his fellow (2014) using three different models which were haloperidol-induced catalepsy, apomorphine-induced morphine behaviour and elevated plus maze model. The results demonstrated a decrease in acetylcholinesterase activity in mice brain and thus proves the anti-amnesic effect of TQ. Besides that, an increase in the levels of thiobarbituric acid reactive substance, glutathione and catalase also proved the anti-oxidant properties of TQ. Moreover, administration of TQ in this study resulted in a decreased level of DA which suggested its antipsychotic-like actions [23].

Another study demonstrated that N. sativa seed possesses the ability to suppress epileptic effects in penicillin-induced epileptic rat models and alters the neurotransmitters monoamine level in some brain regions. From the result, N. Sativa was shown to escalate serotonin level in several areas of the brain and to decrease the DA level in the cortical area [24]. On the other hand, previous studies also investigated the interaction of N. Sativa with neurotransmitter systems. In 2009, TQ was proven to give neuroprotective effects against toxicity induced by 1-methyl-4-phenylpyridinium (MPP+) and rotenone, due to its effect in lowering the level of DA [25].

El-Naggar et al., (2010) in his study also mentioned that the effects of methanolic extract of N. sativa in cultured neurons in-vitro alter the neurotransmitters amino acids release. The study was conducted to observe the sedative and depressive effects of N. sativa in-vitro by evaluating changes in inhibitory or excitatory neurotransmitters amino acids' levels. N. Sativa was found not to induce toxicity to the cells. N. sativa modulates the release of amino acid neurotransmitters by increasing GABA level and decreasing the concentration of glutamate, aspartate and glycine [26].

CONCLUSION

In this review, we highlighted the promising benefits of N. sativa which potentially can be used as a supplement therapy in the management of drug dependence and tolerance. Its main active compound TQ was found to have the ability to modulate the neurotransmitter systems in the brain. Hence, further extensive studies on biochemical, physiological and pharmacological effects of N. sativa on specific drugs are needed in order to develop an alternative natural treatment for drug dependence and tolerance which is safer with lesser side effects.

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Conflict of interests

The authors declared that no conflict of interests based on this study.

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