



# Opioid dependence and substitution therapy: thymoquinone as potential novel supplement therapy for better outcome for methadone maintenance therapy substitution therapy

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## ABSTRACT

Methadone is widely being used for opioid substitution therapy. However, the administration of methadone to opioid dependent individual is frequently accompanied by withdrawal syndrome and chemical dependency develops. Other than that, it is also difficult to retain patients in the treatment programme making their retention rates are decreasing over time. This article is written to highlights the potential use of prophetic medicines, *Nigella sativa*, as a supplement for opioid dependent receiving methadone. It focuses on the potential role of *N. sativa* and its major active compound, Thymoquinone (TQ) as a calcium channel blocking agent to reduce withdrawal syndrome and opioid dependency.

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## Introduction

Methadone is the first widely used drug to overcome the opioid withdrawal effects (1, 2). It acts by occupying the receptor affected by exogenous opioids leading to subsequent receptor activation. Two channels are responsible for opioid withdrawal syndrome, calcium and potassium channel. This activation leads to closing of voltage-sensitive calcium channel (VSCC) and stimulation of potassium efflux causing hyperpolarization and inhibition of adenylyl cyclase activity (3, 4).

Successful approaches to pharmacotherapy in opioid addiction continue to rely largely on substitution of short-acting agonists such as heroin and oral administration of long acting high-efficacy agonists (methadone) or partial agonists (buprenorphine) (5, 6). Notably, all opioids that produce analgesia also can cause tolerance, addiction and withdrawal, and all of the available opioids are misused (7). It was shown that patients on long-term methadone maintenance treatment had longer QTc interval values than expected. Withdrawal symptoms among methadone maintenance therapy (MMT) patients had been reported to become worse and last longer than those of heroin or morphine due to

extremely longer methadone half life (8). Low patient's retention rates in the MMT programme was also reported, making them prone to re-injecting behaviour (9-11).

We believe that calcium channel blocking effect may play a crucial role in opioid dependent and withdrawal syndromes as shown by L-type voltage-dependent calcium antagonist role such as verapamil and felodipine in controlling the withdrawal syndromes effectively (12-15). Both central and peripheral mechanisms play an important role in attenuating opioid withdrawal syndrome via calcium channel blocking agents (16). The effects produced by calcium channel blockers are proven to be independent from opioid receptor sites as there is no agents that can replace naloxone from its binding sites (17). One study has reported that blockade of L-type voltage-dependent calcium channels by calcium channel blockers is responsible for the attenuation of morphine withdrawal (18). Other than that, T-type voltage dependent calcium channels have also been shown to play a critical role in the development of morphine dependence and withdrawal (19).

Previous study reported medicinal plants, *Nigella sativa*, a scientific name for Islamic Prophetic

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medicine, Habbatus Sauda to have L-type calcium channel blocking effect (20). Moreover, further study had also introduced its seeds as a novel treatment for opioid dependence and proven effective in long term treatment of opioid dependence (21).

This plant has green to blue flowers with small black seeds and grows natively in temperate and cold climate areas. The seed of *N. sativa* possesses a source of the main active ingredients such as thymoquinone, monotropens-like P-cymene and  $\alpha$ -pinene, nigellidine, nigellimine, and saponin (22-26).

Considering its low toxicity (27-29), we hypothesized that the main active compound of *N. sativa*, Thymoquinone (TQ), has a role in treating opioid withdrawal syndrome. Many therapeutic potential of TQ have been reported in a variety of medical conditions. TQ also exhibits calcium channel blocker properties via gut spasmolytic, tracheal, and airway relaxant, vasodilator and relaxant activities on the cardiac muscles (30). Thus, further study is needed in order to explore the biochemical effects and mechanism of action of *N. sativa* at cellular level.

## Conclusion

As a conclusion, we would like to suggest probably with the supplementation of *N. sativa* to methadone, it will indirectly be a starting point to answer the question of opioid dependency and withdrawal for better retention of patients in MMT.

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