

Role of oxidative stress in opiate withdrawal and dependence: Exploring the potential use of honey

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ABSTRACT

Opiate dependence and withdrawal is a worldwide public health problem and give a significant burden to society. In exploring the problems of opiate dependence and withdrawal, oxidative stress in thought to be involved in the mechanism of the development of dependence and tolerance to morphine. Therefore, there is possibility that antioxidant has the role to reduce the oxidative stress leading to opiate dependence and withdrawal. In this mini review we describe the evidence of relationship between oxidative stress and opiate dependence. We also describe the evidence of honey which has been claimed to have high antioxidant properties and its promising potential to reduce oxidative stress in opiates dependence and tolerance individuals.

INTRODUCTION

In Malaysia, opiates dependence implicates the country's social and economic development. Harm Reduction Programme was initiated by Malaysia Ministry of Health in 2006, in which Methadone Maintenance Therapy was introduced to be used as a therapeutic method in controlling opioid dependence problems. However, the used of methadone itself would cause dependence and its therapeutic dose had to be increased over the period of time to get the same results (Mattick *et al.*, 2009). Various methods had been used to attenuate opiate dependence including the use of non-addictive materials. These included the use of natural food and plants such as ginger, *Habbatu sauda*, herb roots and many more (Tu *et al.*, 2015; Darvishzadeh-Mahani *et al.*, 2012; Abdel-Zaher *et al.*, 2010). Honey is a natural food produced by bees which provides a lot of benefits to mankind as honey has been used for medicine and as food supplements. Honey bees have been identified to possess

many medicinal values such as anti-cancer; burn wound healing, antibacterial and it also has positive effects on the brain such as to improve memory. This is attributed to the bioactive compounds in honey such as flavonoids and phenolics (Othman *et al.*, 2015; Jaganathan *et al.*, 2014; Alzahrani *et al.*, 2012; Alvarez-Suarez *et al.*, 2012; Al-Waili *et al.*, 2011; Krystyna and Magdalena, 2009; Isabel *et al.*, 2009; Khan *et al.*, 2007).

ROLE OF OXIDATIVE STRESS ON THE MECHANISM OF OPIATE WITHDRAWAL AND DEPENDENCE

Opiate dependence is defined as the need to take opioid at regular interval to avoid withdrawal syndrome. It occurs because of the changes in the brain system especially in the locus coeruleus at the base of the brain. The absence of exogenous opioids will stimulate the locus coeruleus brain cells to release excessive amounts of noradrenaline triggering jittery, anxiety, muscle cramps and diarrhea, increased heart rate, increased blood pressure, widening of pupils and widening of air passages in the lungs as well as narrowing of the blood vessels in non-essential organs. On the other hand, when opiate molecule binds to μ receptors on the brain cells in locus coeruleus, it suppresses the release of noradrenaline resulting in drowsiness, slow respiratory rate and low blood pressure (Kosten and George, 2002).

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There are two mechanisms involved in the development of oxidative stress; formation of free radicals and reduction of antioxidant activity (Mori *et al.*, 2007). The neurotransmitter and gasotransmitters involved in these mechanisms are predominantly glutamate and nitric oxide. Opiate intake affects the mechanism of oxidative stress in the brain. This had been proposed by previous studies which indicated that oxidative stress causes opiate dependency (Mannelli *et al.*, 2009; Abdul Zaher *et al.*, 2013).

It was found that morphine increased the lipid peroxidation in tissues whereas heroin led to oxidative DNA damage, protein oxidation and lipid peroxidation in the brain of mice (Ozmen *et al.*, 2007; Qiusheng *et al.*, 2005). Opioid drugs also exerts effect on the activity of antioxidant systems, as observed by decrease in the total antioxidant capacity in the blood of human heroin addict when compared to the control groups (Pereska *et al.*, 2007). In the experiment with mice exposed to heroin, there was a decrease in the activity of antioxidant enzymes in the brain such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx). Other than that, the ratio of glutathione (GSH) to oxidized glutathione (GSSG) was also decreased, leading to reduction in learning ability of the mice (Guzman *et al.*, 2006). In other studies, Pan *et al.*, (2005) noted a reduction in total antioxidant capacity in the serum and in the antioxidant enzymes, such as SOD, catalase, GPx and elevated markers of oxidative damage of DNA, proteins and lipids in heroin induced mice (Xu *et al.*, 2006). This proposed mechanism was further supported by evidence that pre-treatment with free radical scavengers reducing the symptom of morphine withdrawal syndrome in mice (Abdel-Zaher *et al.*, 2013; Darvishzadeh-Mahani *et al.*, 2012; Abdel-Zaher *et al.*, 2011, Abdel-Zaher *et al.*, 2010). Abdel-Zaher *et al.* (2013) also reported the possible role of oxidative stress and nitric oxide (NO) synthase isoforms in the development of morphine tolerance and dependence, and the effect of alpha-lipoic acid (LA) on these parameters were investigated in mice. They suggested that alpha-LA inhibited morphine-induced oxidative stress and increase the activity of inducible NO synthase in the brain which can attenuate the development of morphine tolerance and dependence. Response to inhibition of morphine-induced NO overproduction and oxidative stress to ameliorate opioid tolerance and dependence was also noted in a study using nigella sativa oil (Abdel-Zaher *et al.*, 2010). Other studies also reported that reduction in oxidative stress will attenuate the development of morphine tolerance and dependence. The studies were done by using thymoquinone for the treatment. Repeated administration of thymoquinone along with morphine attenuated the development of morphine tolerance and dependence, as measured by the hot plate test and assessed by naloxone-precipitated withdrawal manifestations respectively (Abdel-Zaher *et al.*, 2013).

ANTIOXIDANT PROPERTIES OF HONEY

Antioxidant properties of honey are responsible to give balance to a number of antioxidants and free radicals in the body

(Bogdanov, 2010; Bogdanov *et al.*, 2008). Abdel-Zaher *et al.* (2010) reported that reduction in oxidative stress in opiate addicts will reduce dependence and withdrawal symptoms. Looking into this mechanism, honey therefore has a promising effect on the inhibition of morphine-induced oxidative stress which is responsible for the problems of dependence and tolerance in opiate addiction individuals.

Many chronic diseases are linked to the increased oxidative stress caused by an imbalance between liberal-radical production and the antioxidant level. Antioxidants, which are abundant in natural honey, are free-radical scavengers that reduce the formation of or neutralize free radicals (Isnandia Andrea *et al.*, 2013; Letícia *et al.*, 2008). Antioxidant properties of honey had been explored both in *in-vitro* and *in-vivo* studies, in which the authors found that the antioxidant attributes of honey reduced cell damage induced by oxidative stress (Erejuwa *et al.*, 2012).

Diabetes is known as one of the chronic diseases due to oxidative stress. Honey has been used traditionally to treat diabetes. Its antioxidant properties help in reducing free radicals generated as a consequence of the disease process that will ameliorate the patient's general health status. Both studies done using gelam honey and flavonoids showed that the number of reactive oxygen species (ROS) in diabetic induced cell culture decreased and resulted in higher number of living cells. Comparison study on the effects of pure gelam honey and flavonoid on diabetic-induced cell culture resulted in better outcome from the former (Batumalaie *et al.*, 2014; Batumalaie *et al.*, 2013).

The antioxidant content in honey varies depending on its geographical origin (Bogdanov, 2010; Bogdanov *et al.*, 2008). This is because different geographical areas have different types of flowers as the sources of honey production. Honey produced from flowers such as lavender, wild carrot, Manuka and Acasia have been shown to have high antioxidant activity (Alzahrani *et al.*, 2012).

Based on the antioxidant properties, honey therefore can be used as food supplement to improve general health of the body. Studies done by Goon *et al.* (2014) as well as June and Megan, (2012) reported a reduction in DNA damage and antioxidant enzyme activity with the use of honey.

CONCLUSIONS

Chronic used of opiates will cause imbalance between oxidants and antioxidants due to an increase of morphine-induced oxidative stress that leads to the development of dependence and tolerance.

Honey which is claimed to have high antioxidant properties probably has a potential to reduce oxidative stress in opiates dependence and tolerance individuals. This promising potential is therefore becoming the focus of interest in our current study in opioid dependence and withdrawal in order to look deeper into the mechanism and in finding the complementary supplements

of the therapy for the better treatment outcome in opioid dependence and withdrawal.

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