Journal of Applied Pharmaceutical Science Vol. 5 (11), pp. 146-150, November, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.501124
ISSN 2231-3354 (cc) BY-NC-SA

Analgesic effect of honey bioactive compounds and its role in reducing morphine tolerance

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ARTICLE INFO

Article history:
Received on: 29/08/2015
Revised on: 20/09/2015
Accepted on: 11/10/2015
Available online: 27/11/2015

Key words:
Honey, bioactive compound, analgesic , morphine tolerance.

ABSTRACT

Honey has been used as a supplement nutrient in human for centuries. It exerts antibacterial, anticancer, anti-inflammatory properties as well as analgesic activity. But not many studies have been done to analyze effect of honey on morphine tolerance. Hence, this review is targeting on analgesic effect of honey bioactive compounds and their potential in morphine tolerance study.

INTRODUCTION

Honey is a natural supersaturated solution of sugars produced by honeybees. There are different types of honey mainly Manuka, acacia, Gelam, Tualang, rosemary, heather, New Zealand, Australian, Turkish and chestnut honey (Pyrzynska and Biesaga, 2009) with different physical and chemical properties. Honey mainly consists of carbohydrate(95- 98% of dry weight), proteins, minerals and vitamins (White, 1962; White Jr., 1980). As natural liquid, it also contain phenolic acids, flavonoids and alkaloids (Manyi-Loh *et al*., 2011). Carbohydrates, the compound that give main energy source in honey are mainly fructose and galactose, followed by minor constituent of mono-, di- and trisaccharides and oligosaccharides (Sato and Miyata, 2000). In other word, honey contains both complex and simple sugars. Honey can be found in major places of the world. Ancient history marks honey as food and natural remedy used by people in world civilization such as Greeks, Egyptians, Chinese, Romans and Babylonians (Richard, 2009). Today, honey is used for same purposes, traditionally or in modern way.

Bioactive compounds and medicinal properties of honey

Beside sugar as the major content, honey is accumulated with various bioactive compounds which are phenolic acids and flavonoids. Gallic, syringic, benzoic, trans- cinnamic ,p-coumaric and caffeic acids are phenolic acids of honey while catechin, kaempferol , naringenin, luteolin and apigenin and chrysin are the flavonoids (Pyrzynska and Biesaga, 2009). The flavonoids and phenolic acids are known sources of antioxidants that act as free radical scavengers (Johnston *et al*., 2005). Flavonoid also involved in many biological properties such as antibacterial, anti-inflammatory and anti-allergic activities (Gheldof *et al*., 2002). These properties contribute to medicinal values of honey. Many studies suggested honey as good source of natural antioxidants (Ahmed *et al*., 2007).

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More interestingly, honey has same antioxidant activity as in vegetables and fruits based on fresh weight (Gheldof and Engesth, 2002). This important properties contribute to health benefits of honey.

Traditionaly, honey is used to heal wound, sore throat, cough, cold, stomach ulcer and athma (Pyrzynska and Biesaga, 2009; Alzubier and Okechukwu, 2011; Mayer *et al*., 2014). Past and recent researches proved numerous medicinal properties of honey. Other than its power as healing agent, honey play a big role as antimicrobial agent. Manuka and Ulmo honey was shown to give protective effect against Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa (Sherlock *et al*., 2010). Antibacterial properties of honey are also widely studied. Sesamun indicum, honeydew and Turkish blossom honey are examples that posses antibacterial activities (Tornuk *et al*., 2013; Das *et al*., 2015; Mayer *et al*., 2014). On top of that, honey also possesses anti-allergic, anti-inflammatory, antimutagenic, antitumor, antidiabetic and anticancer (Fauzi *et al*., 2011) activities. All of these properties have characterized honey as a versatile natural remedy.

Analgesic effects of honey and potentials in morphine tolerance study

On top of those medical properties widely studied, honey also can act as analgesic agent which is also contributed from its bioactive compounds. Many researchers discovered significant analgesic effects of raw honey (Abdul Aziz *et al*., 2013; Alvarez-Suarez *et al*., 2013; Owoyele *et al*., 2011). For instance, mad honey was found to have analgesic effect which is useful in treating painful diabetic neuropathy (Gunduz *et al*., 2014). Postoperative pain and analgesic requirement also can be reduced by postoperative honey administration (Boroumand *et al*., 2013). In addition 100, 200 and 500mg/kg sidr honey demonstrated dose dependent analgesic effect in acetic acid, formalin writhing test and several other analgesic tests, which prove the honey as a strong analgesic agent (Alzubier and Okechukwu, 2011). However, to date, there are very few studies that relate honey with drug addiction.

Morphine is a commonly used drug in management of acute and chronic pain (Mao *et al*., 2002). Among uses of morphine as analgesic is before surgery, regional anaesthesia and joint pain. However, in morphine abuse, repeated administration of morphine leads to morphine tolerance (Skrabalova *et al*., 2013). Morphine tolerance is a condition in which, the analgesic effect of the drug in the body decreased, causing a higher dose is needed to obtain same analgesic effect (Mayer and Mao, 1999). The analgesic effect of morphine takes part on mu(μ) opioid receptor (MOR), a G protein-coupled receptor (GPCR) on neuron cells. Binding of morphine on MOR causes activation of the G protein and inhibition of adenylyl cyclase. Release of cyclic adenosine monophosphate (cAMP) reduced, causing inhibition of Ca+ and Na+ channels, resulting in analgesia (Kosten and George, 2002; Lees and Lingford-Hughes, 2012; DuPen *et al*., 2007). However in morphine tolerance, the mechanism is still unclear. Nowadays, study suggests opioid receptor desensitization and down regulation as two theories that can explain the phenomenon (DuPen *et al*., 2007). The desensitization of opioid receptor in brain may occur due to prolonged exposure to opioids, by alteration of GPCR (Yoburn *et al*., 2003). Meanwhile, the downregulation of opioid receptor is may due to its internalization by endocytosis, which causes the receptor to be drawn into intracellular environment of neuron cell (Narita *et al*., 2006). Furthermore, previous studies also demonstrated that morphine tolerance leads to increase in oxidative stress (Skrabalova *et al*., 2013). In search for the cure, scientists revealed several cellular processes and conditions that occur in morphine tolerance.

Morphine tolerance among chronic morphine users leads to their continuous needs to morphine administration. To date, methadone therapy is used as a treatment for their morphine addiction (Mohamad *et al*., 2014). However, methadone substitution therapy did not cure tolerance toward morphine. Besides, uses of methadone can cause side effects such as nausea, numbness, insomnia, muscle pain and sexual dysfunction (Goldberg, 2014). Uses of methadone can also lead to addiction, as methadone is addictive. Therefore, a non addictive substance such as honey would potentially functions to reduce morphine tolerance by its various biological properties.

Bioactive compounds such as phenolic acids and flavonoids can give antinociception or analgesic effect. However, not all the compunds that showed analgesic effects participate in opioid system. For example, baicalin demonstrated significant analgesic effect under chemical antinociception in mice, but the mechanism that modulate the analgesic effect seems not involved opioid receptor (Meotti *et al*., 2006). On the other side, several compounds were found to involve with opioid system, as their analgesic effects were inhibited by opioid receptor antagonists (Berrocoso *et al*., 2009). Hence, in this review we explore the honey analgesic properties and their roles in treating morphine tolerance by looking through its phenolic acids and flavonoids.

For instant, gallic acid is one of common phenolic acid found in honey. It is the most abundant bioactive compound in Malaysian Tualang honey after the flavonoid catechin (Khalil *et al*., 2011) and also can be found in Australian eucalyptus New Zealand Leptospermum, Acacia, lime, chestnut and heather honey (Pyrzynska and Biesaga, 2009). To date, there are no attempt to relate gallic acid with analgesic and antinociception. However, its derivative gallic acid ethyl ester, was found to cause no significant effect in pain response (Santos *et al*., 1999).

Ellagic acid, not just contain in fruits and vegetables but also found in Australian eucalyptus, New Zealand and Australian Leptospermum, thyme, rosemary, orange and sunflower honey (Pyrzynska and Biesaga, 2009). Acetic acid writhing test using ellagic acid (0.3-10 mg/kg) showed significant analgesic effect. Furthermore, 1-10 mg/kg ellagic acid was found to have analgesic activity in hot plate test. This test use short thermal(heat) stimulus and can be applied in assessing central antinociception (Kruger, 2001; Schildhaus *et al*., 2014). Thus, compound that give high analgesic effect in hot plate test can be classified as strong

analgesic (Vidyalakshmi *et al*., 2010). In addition, this dose also possessed important analgesic properties, in which coadministration with morphine significantly blocked development of morphine tolerance (Mansouri *et al*., 2014). However, the potential of ellagic acid in treating opioid addiction is still elusive. The reason is because, in this study, it is demonstrated that repeated administration of ellagic acid caused decrease in antinociception and development of tolerance. As the action of ellagic acid on opioid receptor is not confirmed, there are several factors that contribute to the analgesic effect and attenuation of morphine tolerance development. First, Ellagic acid may interact with endogenous opioids such as endorphins, enkephalins and dynorphins, leading to analgesic tolerance after repeated administration. Plus, the role of ellagic acid as free radical scavenging agents is another property that led to attenuation of morphine tolerance (Abdel-Zaher *et al*., 2010). Thus we cannot claim that the attenuation of morphine tolerance was due to action of ellagic acid on mu opioid receptor. Moreover, antidepressant-like activity of ellagic in mice was also found not related to opioid system (Mansouri *et al*., 2015).

Not only contain in honey, caffeic acid are commonly found in fruits and grains. It is known for its anti-inflammatory properties (Chao *et al*., 2009; Liu *et al*., 2014). In a study of inflammatory pain , caffeic acid administered orally by mice showed significant analgesic effect in acetic acid-induced writhing test at doses 5, 10, 30 and 100mg/kg (Mehrotra *et al*., 2011). Tail flick and hotplate test did not show significant thermal antinociception at 30, 100 and 200 mg/kg compared to vehicle treated group. However, in another study of analgesic activity, 10 mg/kg of caffeic acid showed significant tail flick latency (Gamaro *et al*., 2011). Analgesic effect of caffeic acid was also tested with formalin-induced nociception. Formalin test, one of the method to measure ability of a substance to prevent moderate continuous pain generated by injured tissue (Higgs *et al*., 2013). Treatment of 5, 10, 30 and 100 mg/kg caffeic acid did not give any prevention at the early phase (neurogenic). However, at late phase (inflammatory), the antinociception was significantly increased.

Chrysin is a common flavonoid of propolis , honey and plants. Protective effect against cancer, antitumor, antihypertensive, anti-inflammatory and antiapoptotic effects are among biological properties of chrysin (Samarghandlan and Borji 2014; Shin *et al*., 1999). Previous study showed that chrysin cause analgesia at same effect as morphine. Besides, formalin test carried out prove significant analgesic effect of chrysin (50 and 100 mg/kg) at later phase. 150mg/kg chrysin however, showed significant analgesic effect at both early and late phase of formalin test. These results indicate that chrysin analgesic properties might affect like centrally acting drug (Bannon and Malmberg, 2007). Besides, analysis of noradrenalin and corticosterone level in serum also showed significant reduction in chrysin treated-rats, indicating low nociception or pain (Farkhondeh *et al*., 2015).

To date, there is no research conducted to investigate potential effect of apigenin in reducing morphine tolerance. However, apigenin showed analgesic activity and possible relationship to opioid system. Based on analgesic study of Orbignya speciosa Mart., apigenin isolated from dichloromethane extract of the plant showed significant analgesic effect in acetic acid-induced writhing test, similar to morphine-treated mice (Martins Gomes Pinheiro *et al*., 2012). Analgesic effect was also observed on mice in formalin test, in which the effect was similar with morphine–treated mice at first phase of the test. Furthermore, hot plate test conducted on mice treated with opioid receptor antagonist (naloxone) before injection of dichloromethane extract or apigenin showed reversal of analgesic effect. This shows that the effect of apigenin and dichloromethane extract (which also contain apigenin) may have involved in opioid system. Thus, apigenin can be potential compound in treating morphine tolerance.

Quercetin is another common bioactive compound in honey, as it is the most abundant flavonoid in plant. In a study of morphine tolerance and dependence, quercetin showed inhibition of analgesia by naloxone (Naidu *et al*., 2003). Ability of quercetin to reverse morphine tolerance was also proved by chronic treatment of quercetin. 25 and 50 mg/kg quercetin together with morphine reversed the tolerance to analgesic effect of morphine. More interestingly, in attempt to find out possible mechanism underlying the reversal of tolerance, result indicated that the reversal might due to suppression of nitric oxide synthase activity and thus reducing production of nitric oxide. Previous research also had shown that quercetin downregulate expression of nitric oxide synthase (Raso *et al*., 2001).

Other than in citrus fruits, naringenin also contain in honey. Study reports naringenin to have analgesic effect in inhibiting neuropathic pain on rats (Kaulaskar *et al*., 2012; Hu and Zhao, 2014). The result also demonstrates that narigenin reduced lipid peroxidation and nitric oxide. However, there is no study carried out to investigate possible opioid-related action of naringenin and its ability to reduce morphine tolerance. Luteolin, another flavonoid contain in honey, are reported to have analgesic activities in acetic acid-induced writhing and formalin test (Carvalho and Carvalho, 2001). Plants extract of *Cassia siamea* Lam containing luteolin showed significant analgesic effect in hot plate test, in which the flavonoid had contributed to the plant analgesic activity (Ntandou *et al*., 2010). Interestingly, in a study of opioid mechanism of medicinal plant *Vitex agnuscactus* L, it is found that its flavonoid luteolin binded to MOR (Webster *et al*., 2011). This finding is supported by another study of antinociception, in which the analgesic effect of luteolin is blocked by MOR antagonists (Backhouse *et al*., 2008).

CONCLUSION

Honey brings a lot of health benefits to human health by its bioactive compounds. Several bioactive compounds were found to show significant analgesic activities. Some of them are proven to reduce tolerance to morphine. Hence, by these evidences, honey can be a promising natural solution in curing morphine tolerance among chronic morphine users by the synergistic effects of the flavonoids and phenolic acids.

CONFLICT OF INTERESTS

The authors declared no conflict of interest with respect to the authorship and/or publication of thus paper.

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How to cite this article:

Zakaria NH, Ahmad NZ, Hashim SN, Mohd Adnan LH, Shariff MHM, Mohamad N, Mat KC, Abu Bakar NH. Analgesic effect of honey bioactive compounds and its role in reducing morphine tolerance. J App Pharm Sci, 2015; 5 (11): 146-150.