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The Roles of Honey in Male and Female Reproductive Health and Fertility

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Complementary and alternative medicine is widely used and rapidly growing in developing and developed nations. Honey is an important and unique natural product that has been used since ancient times as a therapeutic agent. Recently, attention has been increased toward its use for the prevention and treatment of numerous diseases as well as for improving and maintaining overall well-being. Traditionally, the consumption of honey is a common practice in some cultures as they believe that honey can enhance fertility and vitality. The efficacy of honey in promoting male and female reproductive health and treating fertility-related problems has been evaluated in experimental studies and clinical trials. The prime goal of this review is to highlight the importance of honey in male and female reproductive health by summarising the data collected from both experimental studies and clinical trials on the role of honey in male and female reproductive health.

Keywords: Honey; Reproductive health; Infertility

I. INTRODUCTION

Complementary and alternative medicine is widely used and rapidly growing in developing and developed nations. It is used by 70% of Canadians, 48% of Australians, 42% of the United States population and 80% of the African population. In China, traditional medicine constitutes 40% of the health care delivered. In Malaysia, US$500 million is spent annually for this kind of care. The wide use of traditional medicine is attributed in developing countries to its affordability and accessibility, in Asia due to historical and cultural beliefs; whereas, in developed countries the main cause of the increasing use of complementary and alternative medicine is the concern about the side effects of conventional medicine (WHO, 2002).

Honey is an important and unique natural product. It has been used since ancient times as a therapeutic agent. Recently, attention has been increased toward the use of honey in prevention and treatment of numerous diseases as well as for improving and maintaining overall well-being (Azman *et al.*, 2021; Palma-Morales *et al.*, 2023). The medicinal importance of honey has been introduced in several previous studies. It has been reported to have antioxidant activity (Alfarisi *et al.*, 2020; Alvarez-Suarez *et al.*, 2010), anti-inflammatory activity and antihyperlipidaemic effect (Mohamed *et al.*, 2019) among many other therapeutic importance (Alfarisi *et al.*, 2021; Mohamed & Alfarisi, 2017). Traditionally, the consumption of honey is a common practice in some cultures as they believe that honey can enhance fertility and vitality (Abdul-Ghani *et al.*, 2008; M. Mohamed *et al.*, 2012).

II. DEFINITION AND COMPOSITION OF HONEY

Honey is a natural sweet substance produced by *Apis mellifera* bees from the nectar of plants or from secretions of living parts of plants or excretions of plant-sucking

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insects on the living parts of plants, which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store and leave in honeycombs to ripen and mature (The Council of The Europian Union, 2001). The phytochemical composition of honey varies depending on its floral source, and influenced by seasonal and environmental factors, processing conditions, type of honeybee subspecies and geographical origin (Alvarez-Suarez *et al*., 2014; Kumazawa *et al*., 2012; Zhou *et al*., 2015). Its quality depends on its sensorial, physicochemical and microbiological characteristics (Alvarez-Suarez *et al*., 2010). Thus, the composition and biological properties of honey differ depending on the producing bee species and the location of collection (Sousa *et al*., 2016). The quantitative and qualitative properties of honey constituents are powerful indicators of its botanical and geographical origin (Ciulu *et al*., 2011). Honey is an important and unique natural food product containing as many as 200 components. Its bioactive constituents derived from bees and plants (Ramanauskiene *et al*., 2012). It is a hyperosmotic supersaturated sugar solution owing to high concentrations of monosaccharides. In almost all types of honey, the main constituent is fructose (38%), followed by glucose (31%) (Alvarez-Suarez *et al*., 2010; Chanchao, 2009). It also contains disaccharides and oligosaccharides (Eteraf-Oskouei & Najafi, 2013). Carbohydrates constitute 95% of honey dry weight and they are its main constituents (Bogdanov *et al*., 2008). Honey contains amino acids such as proline, phenylalanine and aspartic acid. It contains 18% water, minerals, vitamins (thiamin, pantothenic acid, pyridoxine, niacin, riboflavin), pollen, proteins (Varsha *et al*., 2015), organic acids (gluconic acid, acetic acid), lipids, volatile chemicals, phenolic acids, flavonoids, carotenoid-like substances (Moniruzzaman *et al*., 2013) and enzymes mainly glucose oxidase and catalase, which are the principle enzymes participating in the major biological activities of honey (Zainol *et al*., 2013), in addition to invertase and phosphatases (Moniruzzaman *et al*., 2013). The mineral contents of honey range between 0.04-0.2% depending on the type of honey. Dark honeys have higher mineral concentrations than the light colour types. About 27 mineral elements have been determined in honey produced in nine different countries (Vanhanen *et al*., 2011). Flavonoids (flavonols, flavanols and flavones) followed by phenolic acids (benzoic acids, phenylacetic and hydroxycinnamic acids) represent the phenolic components of honey (Alvarez-suarez & Giampieri, 2013). Almost all honeys all over the world share the same types of phenolic acids, including caffeic, ellagic, ferulic and p-coumaric acids; flavonoids, such as apigenin, chrysin, galangin, hesperetin, kaempferol, pinocembrin and quercetin; and antioxidants, such as tocopherols, ascorbic acid, superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) (Rao *et al*., 2016). Honey is assessed by analysis of its constituents, which are of great importance for honey industry. These constituents can affect the nutritional and medicinal values of honey and also affect its storage, texture and flavour (Iftikhar *et al*., 2011). The criteria that specify the physicochemical quality of honey are determined by the European Council (EC) Directive 2001/110 and Codex Alimentarius standards and include sugars content, moisture content, water-insoluble content, electrical conductivity, free acid and diastase activity and hydroxymethylfurfural content (HMF) (Codex Alimentarius commission, 2001; The Council of The Europian Union, 2001). Codex Alimentarius standards are valid for honey trade all over the world, whereas European honey regulations are regional standards established based on the regional requirements that may differ from Codex Alimentarius (Bogdanov *et al*., 1999).

III. INFERTILITY

Infertility is a common problem affecting one of six couples during their reproductive age (Chavarro *et al*., 2007). Worldwide, 50 to 80 million people with approximately 48.5 million couples are suffering from infertility, which contribute to 10-15% (Kitchen *et al*., 2017; Prasad *et al*., 2015). In 25%-30% of infertility cases, male factors are found to be the sole cause of the problem. In 40%–50% of the cases the aetiology is female related (Agarwal *et al*., 2005). The combination of male and female factors constitutes toward 30% of the infertility cases (Hammoud *et al*., 2006). The prevalence of infertility is higher in underdeveloped than in developed countries due to poor diagnostic and therapeutic options in underdeveloped countries (Hamad Mohamed *et al*., 2020).

Infertility has negative impacts on the quality of life where it represents a significant psychosocial burden to the affected couples or individuals (Kitchen *et al.*, 2017). The rise in the prevalence of infertility, high costs of medical care with possibility of treatment failure accompanied by public concern about the rising of the adverse effects of the conventional medicine, such as gynecomastia, acne, decreased libido, elevated liver enzymes, reduced bone mineral density, increase in the total body fat and weight gain, increase the risk of female cancer with some fertility drugs, ovarian hyperstimulation syndrome, ovarian torsion and ectopic and heterotopic pregnancy as a complication of assisted reproductive technology, in addition to birth defects, sex chromosome abnormalities, reduced cognitive development and developmental delay in children born with assisted reproductive technology—have motivated the identification of effective treatment with less if not free of side effects (Baron *et al.*, 2013; Chavarro *et al.*, 2007; Dabaja & Schlegel, 2014; Ghazeeri *et al.*, 2012; Hung *et al.*, 2016; Khorram *et al.*, 2001; Michael *et al.*, 2015). Honey is one of the natural products that have been investigated. To evaluate the efficacy of honey in promoting male and female reproductive health and treating fertility-related problems, numerous studies have been conducted experimentally and clinically.

IV. ROLES OF HONEY IN MALE REPRODUCTIVE SYSTEM AND FERTILITY

A. Experimental Research

From an experimental point of view, Mohamed *et al.* (2012) suggested that if honey is used at appropriate dose, it may enhance male fertility. This suggestion emerges based on a study conducted to determine the effect of different doses of Malaysian honey on reproductive parameters in adult male rats. Among three different doses, treatment of rats with Tualang honey at a dose of 1.2 g/kg increased sperm count, which was attributed to enhancement of spermiogenesis as there was no observed effect on spermatid count and reproductive hormones. Based on the achieved improvement of sperm quality parameters in adult male Wistar rats, Igbokwe and Samuel (2013) reported that honey serves as a potential fertility booster. Treatment of white albino male rats with Palestinian honey at 5% concentration selectively increased epididymal weight and epididymal sperm count with stimulation of spermatogenesis through decreasing testicular lactate dehydrogenase (LDH) and increasing sorbitol dehydrogenase (SDH), which are key enzymes in spermatogenesis and maturation (Abdul-Ghani *et al.*, 2008). Sorbitol dehydrogenase converts sorbitol to fructose, which is an energy source for spermatozoa. Fructose metabolism for energy production is faster than that of glucose. Additionally, the by-product of the SDH reaction, NADH, serves as electrons donor to the electron transport system to synthesise adenosine triphosphate (ATP) (Kobayashi *et al.*, 2002). Administration of Gelam honey to healthy male Sprague-Dawley rats was potentially useful in increasing fertility of male rats by increasing sperm count, percentage of normal sperm and reducing percentage of sperm head and tail abnormalities. Testicular histological sections of those rats demonstrated densely packed spermatogenic cell layer with lumen loaded with sperm tails indicating enhancement of spermatogenesis. It has been proposed that honey may act as a physiologic modulator of spermatogenic cell proliferation, which influences the cell cycle of the seminiferous epithelium and increases spermatogenesis (Syazana *et al.*, 2011). The advantageous effect of honey in alleviation the harmful effects of some environmental toxins and diseases on male reproductive system has also been evaluated. Treatment of male rats exposed to cigar smoke (CS) with Tualang honey attenuated the detrimental effects of CS on the rat's reproductive system. It improved spermatid and sperm count, daily sperm production, percentage of motile sperm, percentage of normal sperm morphology and testosterone level. Since the improvement in testosterone was not accompanied by changes in gonadotropins, it has been speculated that the improvement in sperm parameters was owing to the effect of honey on testicular tissue (Mahaneem *et al.*, 2011). This suggestion has been further studied by the same researchers who reported that Tualang honey has the ability to attenuate testicular degeneration caused by the toxic effect of cigarette smoke in rat model. It improved histological abnormalities of seminiferous tubules and Leydig cells of testes. Honey also reduced testicular oxidative stress by reducing lipid peroxidation, which is the likely cause of testicular damage by CS and restored testicular antioxidant system. It has been

suggested that the reduction in testicular oxidative stress by honey administration provides a possible explanation of the improvement in testicular structure (Mohamed *et al.*, 2011). To further support the importance of honey for male reproductive health, Aisyah *et al.* (2011) reported that Gelam honey has the ability to improve fertility in nicotine-treated male rats through improving sperm concentration, percentage of motile sperm and number of morphologically normal sperm. Consistent results have been demonstrated by Noorhafiza *et al.* (2013), who observed that Tualang honey treatment ameliorates the toxic effects of nicotine on spermatogenesis in nicotine-treated male rats. Another work has been undertaken to determine the effect of Nigerian honey on sperm parameters and testes in rats fed with a high sucrose diet. Treatment with honey increased testicular and epididymal weights, sperm count, sperm motility, and percentage of sperm with normal morphology, and reduced the occurrence of sperm with abnormal morphology. It reduced serum levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH), increased serum testosterone and enhanced testicular catalase enzyme (Oyelowo *et al.*, 2014). In rats exposed to noise stress, levels of FSH and LH increased, whereas testosterone level decreased significantly after the exposure. Supplementation of these rats with honey improved testosterone level and decreased FSH and LH levels. The authors suggested that honey beneficial effects on neuroendocrine gonadal axis and testicular cells could be due to its antioxidants activities that can neutralise testicular injury (Kenani *et al.*, 2015). Furthermore, administration of honey to noise-exposed rats enhanced spermatogenesis and sperm viability via abating apoptosis and necrosis of testicular cells that induced by noise stress, which possibly due to the antioxidant properties of honey that can neutralise the patterns of expression of apoptosis-related genes and proteins or controlling anti-apoptotic patterns (Hemadi *et al.*, 2013). The beneficial effect of honey on male reproductive system was also demonstrated by Michael *et al.* (2015) on diabetic and nondiabetic rats. Feeding of these rats with honey-based diet resulted in an improvement in sperm count and morphology with an elevation in testosterone level, both in diabetic and non-diabetic rats. This improvement was supported by the histological examination of testicular tissue which illustrated that the lumen of seminiferous tubules was densely packed with spermatogenic cells with numerous sperm tails in honey supplemented groups compared to the normal diet groups. This testicular architecture indicates enhancement of spermatogenesis in the groups that received honey-based diet. Moreover, addition of 10% of honey to IVF media was found to improve sperm progressive motility and post-insemination pregnancy rate in mice (Hadi, 2017). Honey is a source of glucose, fructose, minerals and vitamins that stimulates sperm motility. Glucose and fructose are considered to be a fuel source for sperm motility (Hadi, 2017). Not only this, an improvement in male reproductive system including increase in testicular and epididymal weights, enhancement of sperm motility and an improvement in the percentage of abnormal sperm were demonstrated in male offspring of female rats exposed to restraint stress when they received honey supplementation in the prenatal period (Haron & Mohamed, 2016). In recently published works, a mixture of three types of honey has been formulated into a single product given the name of Trihoney. Protective effect of Trihoney on hypercholesterolemia-induced male reproductive disturbances has been assessed from different aspects. Trihoney exhibited its ability to maintain testicular integrity and augment spermatogenesis (Mohamed *et al.*, 2020). It optimises neuroendocrine gonadal axis (Hamad Mohamed *et al.*, 2020), improves sperm parameters (Mohamed *et al.*, 2021), and ameliorates hypercholesterolemia-induced epididymal histopathological changes (Mohamed *et al.*, 2020). The lipid-lowering and antioxidant characteristics have been suggested as the main possible mechanisms which drive the improvement of the testicular tissue (Mohamed *et al.*, 2020). The improvement of testicular tissue increases testosterone production, which in turn, decreases FSH through the negative feedback mechanism. Improvement of testicular tissue can also increase inhibin B secretion, which reduces FSH. The hormonal improvement was also suggested to be via the anti-inflammatory mechanism of Trihoney that reduced serum inflammatory biomarkers with a subsequent elevation in serum testosterone and reduction of FSH, through the negative feedback mechanism of testosterone (Hamad Mohamed *et al.*, 2020).

B. Clinical Research

Midcycle pericoital intravaginal application of a mixture of honey and royal jelly in infertile couples, in whom asthenozoospermia is the main cause of infertility, produced a higher pregnancy rate than intrauterine insemination. The exact mechanisms for these achieved results have not been elucidated; however, they have been suggested to be due to the high fructose content of honey that is a well-known energy source for sperm. Additionally, the amino acids and nitric oxide constituents of honey are important for sperm motility, capacitation, and acrosome reaction (Abdelhafiz & Muhamad, 2008). Usage of Tualang honey at a dose of 20g/day in oligospermic men for 12 weeks resulted in an improvement of sperm parameters in terms of concentration, motility and morphology. The effect of Tualang honey was comparable to that of Tribestan (Ismail *et al.*, 2014). Addition of 10% of honey to cryoprotectant medium for sperm preservation resulted in an enhancement of sperm quality after thawing (Fakhrildin & Alsaadi, 2014). The valuable effect of honey was also demonstrated during long-term high-intensity exercise, which is known to increase seminal inflammatory and oxidative stress markers and negatively influenced sperm parameters. Supplementation of road cyclist with 70g of honey one and half an hour before cycling resulted in a reduction in seminal levels of IL-8, IL-1B, IL-6, TNF-α, MDA and ROS, and an increase in seminal antioxidant enzymes activity with significantly less reduction in semen volume and sperm parameters compared to those who did not receive honey (Tartibian & Maleki, 2012). Figure 1 illustrates roles of honey in male reproductive health and fertility.

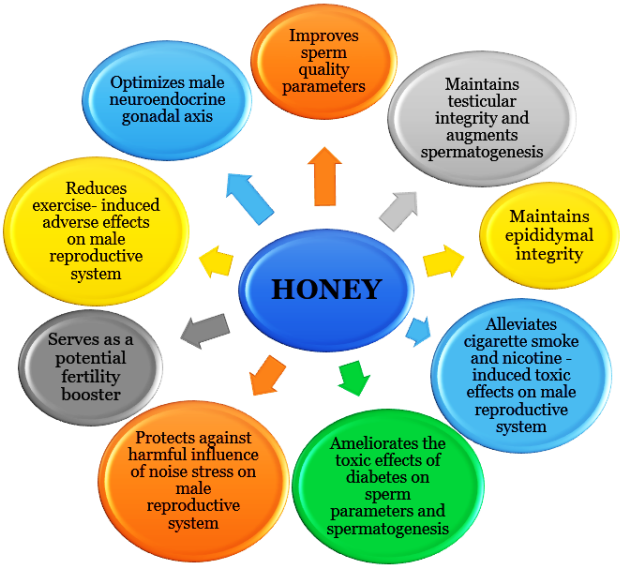

Figure 1. Roles of honey in male reproductive health and fertility

V. ROLES OF HONEY IN THE FEMALE REPRODUCTIVE SYSTEM AND FERTILITY

A. Experimental Research

Administration of Tualang honey for 2 weeks to ovariectomised rat, the animal model of menopause, produced a complete reversal of the vaginal atrophy and maintained the thickness of the endometrium through increase the amount of collagen in the endometrial stroma. There was also vacuolation of vaginal epithelial cells, which reflects an increase in the mucopolysaccharidosis, a beneficial effect for women who are affected by vaginal dryness after menopause. These positive influences of honey have been attributed to the estrogenic activity of its flavonoid constituents in particular to kaempferol and quercetin. Furthermore, flavonoids have antioxidant activity that protects against destructive chemical reactions through their ability to scavenge oxidants and free radicals. The hormonal profile of the honey-treated ovariectomised rats showed an increase in testosterone and progesterone and a reduction in estradiol. The reason for these heterogeneous findings was assumed to be due to the short duration of honey supplementation. Additionally, Tualang honey was able to restore the trabecular thickness in tibial bone, diminished food intake and prevented body weight gain of ovariectomised rats (Zaid *et al.*, 2010). The reduction in the food intake was likely due to the energy provided by honey

as every 100g of honey gives 300 Kcal (Alvarez-suarez & Giampieri, 2013). Similar results to Tualang honey were observed with administration of Gelam honey to ovariectomised female rats. Gelam honey attenuated uterine and vaginal epithelial atrophy and increased the thickness of the uterine endometrial stroma and endometrial surface endothelial layer (Ismail *et al.*, 2021). Honey supplementation to female rats exposed to jumping exercise with different intensities reduced the increase of cortisol, increased relative uterine weight and increased progesterone, which reduced by exercise, with no detectable effect on estradiol level. The increase in progesterone was explained by the protective effect of the carbohydrates and antioxidant constituents of honey against negative energy balance and oxidative stress induced by jumping exercise (Mosavat *et al.*, 2014). As far as the toxic chemicals are of concern, Tualang honey showed its effectiveness in alleviation of Bisphenol A (BPA)-induced ovarian toxicity in prepubertal rat via reducing ovarian morphological abnormalities and reducing number of atretic follicles with protection against oestrous cycle disruption. Honey exerted its protective effects via their estrogenic properties through its bioactive molecules, Quercetin and kaempferol, which share structural similarities with 17β-estradiol (Zaid *et al.*, 2014). Daily treatment of cadmium exposed- female sprague dawley rats with Tualang honey at a dose of 200mg/kg played a favourable role in protection against cadmium-induced ovarian toxicity, which has been manifested by reducing the number of atretic follicles, reducing ovarian morphological abnormalities, restoring gonadotropin hormones, reducing lipid peroxidation and improving antioxidant enzymes in the ovarian tissue (Ruslee *et al.*, 2020).

B. Clinical Research

A randomised prospective clinical study has been conducted to determine the effects of Tualang honey, in comparison with hormonal replacement therapy (HRT), on 79 postmenopausal women for a period of 4 months. Among the several parameters of the study, the hormonal profile has been evaluated. Administration of 20g of Tualang honey on daily basis reduced blood levels of LH and testosterone in a comparable effect to HRT. However, no significant changes were observed in the FSH and oestradiol level (Nik Hussain *et al.*, 2012). In a clinical trial conducted to determine the effect of honey on dysmenorrhea, pure honey showed its effectiveness in prevention and treatment of dysmenorrhea-associated headache, nausea and vomitting (Ajorpaz *et al.*, 2012). Effectively, pure honey exhibited its advantageous role in reducing pain and amount of bleeding in women suffer from primary dysmenorrhea (Ajorpaz *et al.*, 2012). Honey inhibits growth of candida albicans, but it had no effect on lactobacillus, which is a natural vaginal flora. Hence, it has been suggested as a treatment for vaginal candidiasis without affecting vaginal normal flora (Banaean-Boroujeni *et al.*, 2010). Goli and his colleagues conducted a randomised clinical trial on 106 women confirmed with vaginal candidiasis. They apply honey gel in one group in comparison with clotrimazole cream in the second group. After eight days of treatment, clinical examination and culture have been re-evaluated. Honey exhibited its effectiveness in the treatment of vaginal candidiasis with additional advantage of increasing lactobacilli compared to before treatment (Goli *et al.*, 2017). In the same year, Banaeian and his coworkers conducted a similar clinical trial on eighty women diagnosed with vulvovaginal candidiasis. Honey ointment was applied to the women in one of the two assigned groups and clotrimazole ointment in the other group. Honey treatment improved the inflammation and vaginal discharge, however, to a lesser extent than clotrimazole. There was no difference in irritation severity and satisfaction with treatment between the two groups with no side effects have been reported (Banaeian *et al.*, 2017). The beneficial effects of honey in female reproductive health and fertility are summarised in Figure 2.

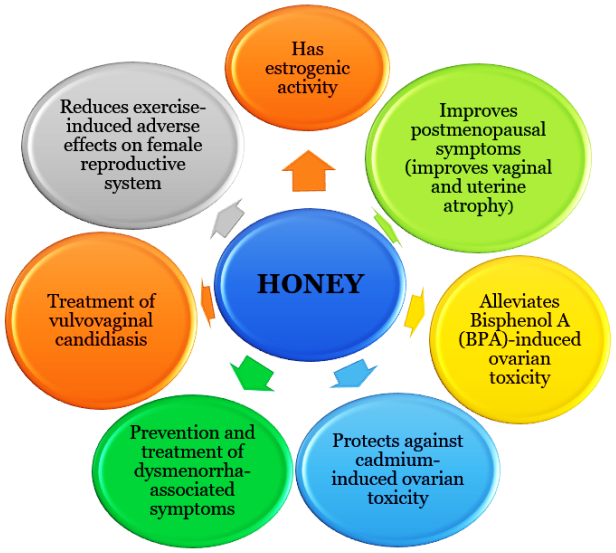

Figure 2. Roles of honey in female reproductive health and fertility

VI. CONCLUSION

Honey effectively maintains testicular and epididymal integrity, augments spermatogenesis and improves sperm quality parameters. It optimises male neuroendocrine gonadal axis and reduces exercise-induced harmful effects in male reproductive system. Honey alleviates cigarette smoke-, nicotine-, noise stress- and diabetes-induced toxic effects on male reproductive system. It serves as a potential male fertility booster. In females, honey prevents and treats dysmenorrhea-associated symptoms, treats vulvovaginal candidiasis, reduces exercise-induced adverse effects on female reproductive system. It alleviates Bisphenol A and cadmium-induced ovarian toxicity. It improves postmenopausal symptoms. These important roles of honey need further evaluation, particularly with clinical trials to determine the time of initiation of honey treatment and the exact dose required.

VII. CONFLICT OF INTEREST

The authors declared no conflicts of interest.

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