



Review of the multifaceted health benefits of Malaysian honeys: Impacts on pregnancy

Nur Anissa Vidka Anjani and Wan Ezumi Mohd Fuad*

Programme of Biomedicine, School of Health Sciences, Universiti Sains Malaysia,
Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia

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Honey has been utilised as traditional medicine due to its variety of health benefits. Both flavonoids and phenolic content in honey possess numerous health advantages, such as antioxidant, anti-inflammatory, and antibacterial properties. Malaysian honeys such as kelulut honey (KH), tualang honey (TH), gelam honey (GH), acacia honey (AH), and pineapple honey (PH) are reported to exert positive effects towards the female reproductive system, particularly on hormonal regulation and protection against harmful materials that could lead to infertility. The nutritional compounds in Malaysian honey, including vitamin B6, iron, folate, fructose, and other minerals, are found to have positive effects on anatomical and physiological changes during pregnancy, such as reducing nausea and vomiting, improving pre-eclampsia, iron deficiency anaemia, neural tube defects, and gestational diabetes mellitus. Moreover, consuming Malaysian honey can also serve as a preventive measure against urinary tract infections during pregnancy. Previous studies have mentioned the benefits of Malaysian honey, but only a few have discussed its advantages on the female reproductive system and pregnancy. Therefore, this review aims to provide a comprehensive literature review, with a focus on the advantageous roles of chemical compositions in Malaysian honeys during pregnancy and their impacts on the female reproductive system.

Keywords: Flavonoids, Health benefits, Malaysian honey, Phenolic acids, Polyphenols, Pregnancy

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Introduction

Pregnancy is defined as the period in which a foetus develops inside a woman's uterus, with an average pregnancy duration lasting 280 days¹. During pregnancy, the mother experiences major anatomical and physiological changes, including haematological, cardiac, renal, respiratory, and endocrine systems². These changes are necessary to accommodate the developing foetus and prepare for delivery. Furthermore, some physiological changes necessitate supplementary nourishment to enhance fetal growth and the health condition of children during their critical life³. Insufficient supplies of nutrition might be closely associated with the mortality and morbidity of newborns⁴. The nutrition is obtained from a variety of food sources, vitamins, and polyphenol supplementation. Polyphenol is defined as a natural molecule synthesised by plants with chemical properties that relate to phenolic substances⁵. The most significant types of polyphenols are flavonoids

and phenolic acids. Among these, maternal polyphenol supplementation is commonly used for its powerful antioxidant properties⁶. This supplementation can be obtained from fruits, vegetables, nuts, olive oil, and honey⁷. Unlike other types of dietary resources, honey contains various types of polyphenols that can reduce the risk of maternal disease and foetal impairment during pregnancy⁸. The phenolic composition in honey varies between samples, making it a useful indicator for determining the origin of honey⁹.

Malaysia is a tropical country rich in flora and fauna, supporting a dynamic ecosystem that produces a variety of honey¹⁰. Bees are beneficial insects that generate beneficial honey and other medicinal honeybee products. The honeybee evolved from a single genus of *Apis* within the tribe *Apini*, with *Apis mellifera* being the most common subspecies¹¹. In Malaysia, *Apis mellifera* bees produce pineapple honey (PH) and acacia honey (AH) from the collection of nectar from pineapple (*Ananas comosus*) and acacia (*Robinia pseudoacacia*) blossoms, respectively. Other subspecies, the giant *Apis dorsata*

*Correspondent author
Email: wanezumi@usm.my

stinging bees, produce two types of honey. Well-known tualang honey (TH) is harvested from tualang trees (*Kompassia excelsa*), and gelam honey (GH) is collected from gelam trees (*Melaleuca cajuputi*).

Meanwhile, kelulut honey (KH) is produced by *Trigona spp.*, a stingless bee species¹². In general, honey is rich in phenolic compounds, which are strongly correlated with its antioxidant properties. The phenolic compounds are further divided into two subclasses, such as substituted benzoic and cinnamic acids. Meanwhile, flavonoids, which include flavonols, flavones, and flavonones, have a similar structure to phenolic acid¹⁰. Studies have found that natural polyphenol consumption can protect the female reproductive system by modulating the hormonal regulations. Besides that, polyphenols also provide numerous biological properties, such as antibacterial, anticancer, anti-inflammatory, antioxidant, and anti-atherogenic effects¹³. Deficiencies of specific polyphenols may increase oxidative stress, which affects the production of mature oocytes, resulting in infertility¹⁴. Furthermore, decreased polyphenol consumption during pregnancy might cause pre-eclampsia, endometriosis, and PCOS, which lead to poor pregnancy outcomes¹⁵.

A decrease in polyphenols can also be associated with antioxidant deficiency. Additionally, it is also related to a lack of copper (Cu), zinc (Zn), or manganese (Mn) consumption¹⁶. These compounds are necessary for the prevention of pre-term birth, low birth weight, pre-eclampsia, and placental insufficiency¹⁷. Previous research has shown that honey contains abundant amounts of minerals depending on its geographical and botanical origins including major ones (calcium, magnesium, potassium, chlorine, and sulfur) and trace elements such as Zn, Mn, Cu, lead (Pb), titanium (Ti), rubidium (Rb), barium (Ba), cerium (Ce), chromium (Cr), boron (B), strontium (Sr), and mercury (Hg)¹⁸. These types of minerals are broadly present in Malaysian honey. Thus, consuming honey during pregnancy may be recommended to reduce the risk of complications that can occur during pregnancy. Besides phenolic acid and minerals, Malaysian honey is also rich in carbohydrates that primarily consist of fructose and glucose¹⁹. In addition to fructose and glucose, Malaysian honey also contains small amounts of disaccharides and oligosaccharides²⁰. These classes of carbohydrates are mainly responsible for some of the main functional benefits, including the capability to retain moisture, extend the shelf-life, and

promote colour and flavours of honey²¹. During pregnancy, carbohydrate is required for the development of both the maternal and foetal brain.

Additionally, the placenta prefers glucose as its major fuel substrate. Failure to account for placental glucose requirements, combined with reduced carbohydrate intake, could result in an unhealthy intake of these essential nutrients. Malaysian honey also contains different types of vitamins, including ascorbic acid, riboflavin, nicotinic acid, folic acid, and pyridoxin¹⁰. Lack of these vitamins can cause DNA damage and oxidative lesions, which can be hazardous to both the mother and the foetus. Despite its diverse beneficial effects, there is limited information available regarding the impacts of honey during pregnancy.

Variations and physicochemical properties of Malaysian honey

Honey is a viscous amber-coloured fluid produced by the honeybee species. The component of honey is strongly influenced by climatic conditions²². For instance, Indonesia and Malaysia share comparable geographical and climate seasons. Therefore, a significant number of their honeys originate from the same species but are somehow labelled differently²³. Both hilly and plain areas of Malaysia produce a variety of unifloral and multifloral honeys²⁴. According to the melissopalynological analysis, unifloral honey is described as honey produced primarily from a single vegetal nectar source, which accounts for more than 45% of the total pollen²⁵. There are several types of unifloral honey in Malaysia, including GH, PH, and AH.

Regarding physicochemical properties, AH and PH have a distinctive aroma and flavour¹⁰. The distinctive aroma and flavour are mainly due to the origins and volatile compositions of the honey²⁶. Nonetheless, GH is characterised by an amber colour and low viscosity, with a sweet-smelling and slightly acidic taste²⁷.

In contrast, multifloral honey is characterised as a mixture of several different types of nectar that are combined by honeybees when converting stored nectar into honey. TH and KH are the most common multifloral honeys²⁸. Each variety of unifloral and multifloral honey produces diverse physicochemical, polyphenols, and biological activities depending on its floral source. The prominent TH in this country, which is made from multifloral nectars from the tropical rainforest in the northwestern region of Peninsular Malaysia, exhibits a dark brown

appearance with the highest acidity. In comparison to other types of local honeys, KH is slightly more liquid and has a unique sour taste²⁹. It also has a distinct aroma and undergoes slow crystallisation³⁰. There are primary indicators to determine honey quality, such as pH value, moisture content, electrical conductivity, reducing sugar content and hydroxymethylfurfural (HMF)³¹. In terms of pH, all types of Malaysian honey are considered acidic, with pH ranging from 3.53 to 4.03 within the limit of 3.4 to 6.1³². pH of TH is shown to be 3.14 to 3.80, GH 3.38 to 3.83, KH 3.27 to 3.30, PH 3.73 and AH 3.53. These values are similar to honeys originating from India³³, Brazil³⁴, Turkey, and Spain³⁵. High acidity in honey is responsible for the flavour and stability against microbial spoilage³⁶.

The moisture contents of honeys in Malaysia are higher when compared to those of honeys that originate from Europe. This is probably due to the rainy season that occurs throughout the year. However, this moisture content is still considered lower than that from India³³, Anatolia (Turkey)³⁷, Romania³⁸, and Portugal³⁹. Moisture content indicates the amount of water that is present within the honey and contributes to its ability to resist fermentation during storage⁴⁰. A previous study reported that TH and GH contain more than 20% moisture content, which violates the guidelines of the European Honey Legislation and Codex Alimentarius Standards¹⁸. As a result, these types of honey need to be treated with evaporation in order to reduce the water content and improve their quality. However, PH was demonstrated to have the lowest moisture content, indicating that it is the most resistant to microbial proliferation¹⁰. In addition, maintaining a low moisture level is crucial for extending the shelf life of honey. Therefore, it is important to maintain the moisture level below the recommended threshold set by international regulations for honey quality.

Electrical conductivity (EC) is an essential measurement to determine the physical characteristics of honey, including its purity and botanical origin⁴¹. According to the standard set by the Codex Alimentarius (2001), all Malaysian honeys were found to have EC values ranging from 0.35 to 0.76 mS/cm, which are less than the permissible standards of 0.8 mS/cm. Previous studies demonstrated that the EC of AH, KH, TH and GH are in the broad range of 0.75 to 1.89 mS/cm, with KH exhibiting the highest value of 1.89 mS/cm as opposed to PH, which has the

lowest EC value of 0.35 mS/cm³². The EC values measured from these studies are similar to those of honey originating from India, Morocco, Uruguay, Spain, and Andalusia. The EC value lower than 0.8 mS/cm indicates blossom honey, whereas the EC value higher than 0.8 mS/cm indicates honeydew honey⁴¹.

There are many factors contributing to the EC value, such as time, storage, temperature, water content and the concentration of ions and minerals⁴². Malaysian honeys have an average sugar content of $65.53 \pm 2.48\%$ g/mL. The sugar test determines the level of honey sweetness, with fructose being the most abundant sugar⁴³. A previous report found that the total sugar contents of TH, PH, and GH are 63.60% which is lower than AH with an amount of 68.40%. According to this finding, none of the samples surpassed the maximum limit of total sugar content in honey established by the European honey legislation. Meanwhile, the reducing sugar of GH is higher than that of TH (62.17% and 61.94% respectively), while AH concentration (63.89%) is the highest among other types of honey⁴⁴. Nonetheless, other countries such as India and Estonia have comparatively greater sugar concentrations ranging from 78.4 to 82.4% and 62.88 to 78.32% respectively, in comparison with all types of Malaysian honey⁴⁵.

Beneficial effects of polyphenol supplementation during pregnancy

Honey is a natural source of flavonoids, phenolic acid, and its derivatives. Besides honey, polyphenols are also present in apples, broccoli, and onions. Each type of honey contains varying amounts of phenolic acids and flavonoid compounds depending on its botanical origin⁴⁶. A recent study has shown that TH contains the highest phenolic content with an amount of 352.73 ± 0.81 mg/kg, followed by KH, GH, PH, and AH⁴⁷. In contrast, an earlier study stated that KH exhibits the highest phenolic content among other types of honey⁴⁸. The majority of flavonoids and phenolic acids present in food have proven to provide a broad range of biological activities that contribute to health benefits. Therefore, polyphenol supplementation is actively being recommended, especially during pregnancy.

Polyphenol consumption during pregnancy can help to prevent dyslipidemia, restore foetal development, reduce hyperglycemia, and promote systemic and uteroplacental circulations⁵. Furthermore, regular ingestion of flavonoids in enough proportions

can reduce the risk of oxidative stress and the development of chronic inflammatory diseases such as cancer, neurological disorders, and cardiovascular disease (CVD)⁴⁹. Recently, the rising number of CVD patients is primarily due to the occurrence of hypertension during pregnancy. In contrast, the consumption of phenolic acids and flavonoids inhibits maternal prostaglandin during the third trimester⁵⁰. In cardiovascular homeostasis, prostaglandin elevates the blood pressure via activation of the F prostanoid (FP) receptor. FP is expressed in the hypothalamus, renal collecting duct, and preglomerular arterioles. Deletion of FP reduces blood pressure concurrently with the reduction of plasma renin, angiotensin, and aldosterone⁵¹. Therefore, inhibition of prostaglandin during pregnancy can reduce the risk of hypertension and consequently contribute to the decline of cardiovascular morbidity and mortality. Besides the prevention of CVD, polyphenols are also able to prevent the incidence of pre-term birth (PTB) through their antioxidant activities⁵². Furthermore, the prevention of prematurity may be facilitated by the supplementation of antioxidant agents, such as vitamins C and E or other trace elements, such as zinc¹⁶, which are abundantly present in Malaysian honey.

The antioxidant properties present in honey correlate with its colour intensity⁵³. Honey with darker colours appears to have higher antioxidant as well as phenolic contents⁵⁴. The reviewed study shows that KH has the highest antioxidant properties when compared to GH and TH⁴⁸. Nevertheless, another previous study revealed that TH contains the highest antioxidant properties among Malaysian honey¹⁰. This variability occurs due to several different factors, such as humidity, harvest season, and most importantly, the plant family origin. Antioxidant activities within honey are commonly known to neutralise free radicals. Uncontrolled free radicals may lead to the formation of oxidative stress, causing damage to cellular components and resulting in developmental abnormalities or even embryonic death. Human studies have revealed that consuming TH at doses ranging from 0.75 g/kg to 1.5 g/kg significantly increases antioxidant activity and suppresses oxidative stress in female athletes⁵⁵. *In vitro* studies also demonstrated that GH has the ability to reduce oxidative stress and activate the insulin signalling pathway in the pancreatic hamster cells as a prevention for diabetes and hyperglycemia in

pregnancy⁵⁶. The antioxidant properties present within the honey are not only important to neutralise free radicals, but they also contribute to the immunological development by acting as a natural immunomodulator and modulating the immune response to pathogens⁵⁷.

Inflammation is defined as an organic process that changes into a pathological event, resulting in the activation of the immune system, which includes leucocytes and blood plasma⁵⁸. *In vivo* research has shown that propolis, a substance produced by honeybee species, has a huge potential for anti-inflammatory properties. It plays an important role in regulating the components of the immune system⁵⁹. In studies conducted by⁶⁰, it was stated that the consumption of propolis extract from honey can reduce bacterial vaginosis infection in pregnant women. Besides propolis, TH has the ability to control the activities of glutathione-S-transferase (GST) to manage the production of glucose levels. Alteration of GST can cause numerous pregnancy complications, such as pre-eclampsia and gestational diabetes mellitus. In addition to TH, GH also demonstrated a variety of anti-inflammatory properties, such as in the treatment of acute oedema. It inhibits the production of pro-inflammatory cytokines such as interleukin 6 (IL-6), tumour necrosis factor alpha (TNF- α), nitric oxide (NO), and prostaglandin E2 (PGE2) in paw tissues of the rat⁶¹.

Oedema during pregnancy commonly occurs due to increased sodium retention derived from hormones and an enlarged uterus pressing the blood vessels, impairing the circulation from the legs to the heart. However, it can be the signal for serious conditions such as pre-eclampsia or deep vein thrombosis (DVT)⁶². In the pathogenesis of oedema, pro-inflammatory cytokines increase the endothelial damage and vascular permeability, leading to fluid leakage into the tissues. Therefore, a balance between pro-inflammatory and anti-inflammatory cytokines is necessary for the immune tolerance during pregnancy.

Honey has also been demonstrated to play a role in bodyweight reduction during *in vivo* studies. Consumption of PH as low as 6.25% was proven to inhibit the proliferation of adipocyte tissues through a significant reduction of lipid accumulation and size⁶³. This statement is supported by an *in vitro* study conducted by⁶⁴. They claimed that rats fed a honey-based diet substantially reduced their adipocyte size in comparison to those that were not fed a honey-based

diet. Meanwhile, research indicates that women who have a body mass index (BMI) higher than 25% are likely to have a greater risk of miscarriage and other types of complications that could lead to maternal and foetal death⁶⁵. Hence, the consumption of honey during pregnancy should be regarded as a potential component of alternative medicinal supplementation in order to reduce the risk of maternal and foetal complications.

Malaysian honey and pregnancy

Role of Malaysian honey on the female reproductive system

The female reproductive systems are composed of internal and external organs that regulate gamete production, secrete sex hormones, and support the development of fertilised eggs into mature foetuses⁶⁶. The reproduction process commences with the regulation of the hypothalamic-pituitary-gonadal (HPG) axis to achieve ovulation⁶⁷. The first signal is originally derived from the central nervous system (CNS) that stimulates the synthesis of gonadotropin-releasing hormone (GnRH). This hormone is a key regulator that modulates the anterior pituitary gland to produce follicle-stimulating hormone (FSH) and luteinising hormone (LH)⁶⁸. The interference with this hormonal regulation results in a range of disorders that can lead to infertility⁶⁹. Reproductive health and fertility rates have declined for the past three decades⁷⁰. Consequently, the majority of individuals have recently shifted towards alternative and complementary medicines, particularly relying on natural products as dietary supplements and alternative treatments.

Malaysian honeys have traditionally been utilised in a variety of cultures to enhance male and female fertility. In general, honey contains supersaturated acidic solutions in combination with high osmotic pressure⁷¹. This environment is not suitable for the development of bacteria; hence, honey will act as an antibacterial agent and maintain the normal vaginal flora⁷². A recent study has demonstrated that pathogenic changes in microbiota impair the implantation process, resulting in infertility problems¹¹. Therefore, honey is capable of regulating the microbiota of the vagina, which in turn affects the microbiota of the uterus, causing a positive impact on the fertility process⁷³. In Malaysia, traditional practitioners actively utilise honey as an effective ingredient in the production of nutraceutical products such as *majun* and *jamu*. These types of products are believed to improve ovum quality and strengthen the uterus as well as the vaginal wall⁷¹.

Besides Malaysia, the Indonesian populace also uses *jamu* containing various ingredients, including honey, as their traditional medicine that has been perfected since the ancient Javanese kraton palace. Normally, Indonesian women consume *jamu* to relieve menstrual pain and to maintain reproductive health⁷⁴. The efficacy of *jamu* in the context of reproductive health is attributed to a variety of factors, including its antioxidant elements, which are believed to produce remarkable effects. The abundance of antioxidants in honey can have indirect effects on fertility, including ameliorating the stress-depression effects that often accompany reproductive challenges⁷⁵. Understanding fertility issues is crucial, as the interplay between stress and infertility has long been established⁷⁶. Catecholamines like dopamine, adrenaline, and noradrenaline, as well as the hypothalamic-pituitary-adrenal (HPA) axis stress hormone, cortisol, interact with female reproductive hormones such as GnRH, LH, and FSH. This interaction affects the synthesis of melatonin and endogenous opioids⁷⁷. As a result, this disrupts the ovulation process, which in turn influences the function of the reproductive organ. Moreover, the stress-induced HPA activation alters the HPG action by limiting GnRH release from the hypothalamus and inhibiting the secretion of progesterone and LH. This results in the disturbance of the menstrual and ovarian cycle⁷⁸.

A former investigation unveiled that TH is capable of restoring the HPA axis activity through its antioxidant properties in stress-induced rats. The rats were shown to demonstrate a notable reduction in depressive-like behaviour and a corresponding decrease in stress hormone levels following TH administration⁷⁹. Along with TH, AH also demonstrated a substantial impact in reducing the depression effect by regulating the glucocorticoid imbalance⁴⁴. Generally, stress-induced glucocorticoid impairs the function of the HPG axis, contributing to the inhibition of the reproductive system and disruption of female gonadal activities⁸⁰. Excessive exposure to free radicals from multiple sources can also lead to DNA alteration, resulting in abnormal coding of tumour suppressor genes and increasing the risk of developing reproductive-tract-related malignancies in immunocompromised women⁸¹.

Generally, cadmium exposure has been found to have detrimental impacts on the pituitary gland and disrupts the normal synthesis of GnRH⁸². This

interference will result in the reduction of FSH and LH levels and ultimately lead to reproductive issues. Typically, during the follicular phase of the menstrual cycle, FSH stimulates the maturation of ovarian follicles, while LH plays a key role in the ovulation and implantation of a fertilised ovum in the uterus⁸³. Nonetheless, reductions in FSH and LH levels can inhibit the ovulation process and reduce fertility outcomes⁸⁴. Uniquely, TH has been proven to demonstrate substantial effects on the cadmium-exposed rats, potentially contributing to the normalisation of GnRH levels. It is shown that TH could normalise the positive and negative feedback mechanisms present in the ovary, contributing to the production of normal ovarian follicles⁷¹. Besides cadmium, TH has been revealed to have a protective effect against bisphenol A (BPA) exposure. Currently, BPA is considered one of the most extensively utilised chemicals. The majority of BPA products are used in the manufacturing of polycarbonates and polymers⁸⁵. *In vitro* and *in vivo* studies have reported that BPA exposure decreased female fertility due to the disruption of oocyte maturation and the reduction in the synthesis of ovarian oestradiol⁸⁶. In the study conducted by⁸⁷, they discovered that BPA-exposed rats treated with TH have significant improvement in the morphological abnormalities of ovarian follicles when compared to BPA-exposed rats without TH treatment. These findings indicated the ability of TH as a protective mechanism against genotoxic effects induced by BPA. Moreover, consuming TH at a dose of 1 g/kg was also shown to minimise the adverse effect induced by exercise on female reproductive hormones⁸⁸. They discovered that TH exhibited a protective mechanism against structural changes in the uterus and ovary of the jumping exercise-induced rat.

In addition to TH, GH also contains beta-hydroxy ketone, which is considered the central structure of prostaglandin³². Prostaglandin, a part of the C20 group, is synthesised by the arachidonic acid with cyclooxygenase as a key enzyme. It plays a crucial role in mediating gonadotropin activity during ovulation⁸⁹. Aside from prostaglandin, GH also contains a small amount of testosterone hormone⁹⁰. Although this hormone is typically found in males, testosterone possesses a variety of benefits in the female reproductive system, such as preventing sexual dysfunction and protecting the vagina from dryness⁹¹. Moreover, testosterone also acts as an obligatory

precursor for oestradiol synthesis, which is essential for the thickening of the uterine layer during fertilisation⁹². Consuming GH at the dose of 0.2g/kg/day could be utilised as adjunctive hormonal replacement therapy (HRT) to lessen the effect on progesterone and oestradiol⁹³. HRT is extensively utilised in the treatment of post-menopausal women through the administration of oestrogen or progesterone⁹⁴. However, this hormonal administration increases the risk of developing breast cancer and gallbladder stones⁹⁵. Hence, GH can serve as an alternative natural ingredient to be consumed by post-menopausal women, thereby mitigating the side effects of HRT.

Other than HRT-related concerns, polycystic ovary syndrome (PCOS) is another hormonal disorder that profoundly impacts the endocrine, reproductive, metabolic, and psychological systems of women during their reproductive years⁹⁶. PCOS has been recorded to represent approximately 80% of infertility cases among women⁹⁷. The most common medication used to treat PCOS is clomiphene citrate (CC)⁹⁸. CC has been widely used for anovulatory infertility treatment because it is a simple, cheap, and effective method to induce ovulation⁹⁹. It works by binding to oestrogen receptors on the hypothalamus, which in turn stimulates the GnRH pulse. This further induces the secretion of GnRH from the anterior pituitary, leading to the development and maturation of ovarian follicles¹⁰⁰. However, 20-25% of anovulatory women do not respond to CC treatment and are considered to be clomiphene-resistant¹⁰¹.

A study conducted by⁴⁷ revealed that the consumption of KH at a dose of 1 g/kg/day could normalise the oestrous cycle in PCOS rats, which is comparable to clomiphene treatment. Furthermore, animal-induced PCOS has also been demonstrated to have higher levels of testosterone and LH, resulting in the disturbance of steroid hormones. A consumption of KH alone was observed to reverse the testosterone level, whereas a combination of KH with clomiphene was found to reduce the LH levels as compared to clomiphene alone. This study implies that KH and clomiphene exhibit a synergistic effect. Therefore, natural honey supplements could be suggested as a complementary treatment for PCOS to avoid clomiphene resistance. Apart from that, PCOS also raises the tendency of having type 2 diabetes mellitus (DM). Obesity, tension, and differentiation in the primary hormone levels are the main causes of DM

type 2 globally¹⁰². Obese females with PCOS are more susceptible to insulin resistance. Increasing insulin levels lowers the circulating amount of sex hormone-binding globulin (SHBG), which constrains follicle formation, resulting in irregular menses and impotence¹⁰³. GH extract through its phenolic compounds was shown to have positive effects against insulin resistance¹⁰⁴. Moreover, rats treated with KH at the doses of 1.0 and 2.0 g/kg/day for 28 days were proven to exhibit hypoglycemic effects, contributing to a notable improvement in serum insulin levels¹⁰⁵. Thus, the consumption of honey may be recommended as a preventative measure for patients with insulin resistance.

Role of Malaysian honey during pregnancy

Human pregnancy is an intricate and remarkable process that signifies the continuation of human life. The first trimester occurs during the first 3 months of pregnancy and is subdivided into embryonic and foetal development. The second trimester takes place in the middle of pregnancy, from week 13 to 26. The third trimester commences in week 27 and may end in week 40 prior to delivery¹. Throughout pregnancy, a mother's body undergoes profound physiological and anatomical changes to accommodate the development and growth of the foetus². This complex process runs approximately within nine months¹⁰⁶ marked by numerous physiological and hormonal changes¹⁰⁷. In the initial stages of pregnancy, human chorionic gonadotropin (HCG) is synthesised within 10 days of ovulation¹⁰⁸. This hormone stimulates the corpus luteum to secrete a large amount of oestrogen and progesterone to maintain the pregnancy¹⁰⁹. The production of HCG increases for two months as the placenta begins to grow and subsequently declines as the corpus luteum starts to degenerate¹¹⁰. During this period, a pregnant female typically experiences mild to moderate symptoms of nausea and vomiting, commonly referred to as morning sickness or nausea and vomiting of pregnancy (NVP)¹¹¹. The development of NVP is expected to deplete toward the end of the first trimester. Nevertheless, if the condition persists into the second and third trimester of pregnancy, it is imperative to identify alternative causes¹¹². In 0.3-2.3% of cases, NVP progresses to the more severe condition known as hyperemesis gravidarum¹¹³. The World Health Organization (WHO) defines hyperemesis gravidarum as a condition where NVP starts before 22 weeks of gestation, but the onset of symptoms and the time

frame of the symptoms remain unclear. In the most severe case of NVP, it requires hospitalisation and parenteral nutrition¹¹⁴. Moreover, NVP impacts the mother's appetite and causes nutritional deficiency that ultimately leads to undernutrition¹¹⁵. It is imperative to ensure optimum maternal nutrition in early gestation to facilitate foetal growth throughout pregnancy. Therefore, an adequate quantity of nutrients must be consumed to compensate for the nutritional loss caused by NVP.

The most common treatment employed to reduce the intensity of NVP is vitamin B6¹¹⁶. Nevertheless, WHO (2023) has concluded that there is insufficient evidence on the benefits and potential risks of routine vitamin B6 supplementation during pregnancy. Thus, the use of honey as an alternative natural ingredient could be recommended to replace the conventional use of vitamin B6. Honey comprises different types of vitamins, including vitamin B6, niacin, riboflavin, pantothenic acid, folic acid, and ascorbic acid⁸. There is evidence reporting that consuming ginger in combination with Indonesian honey twice a day significantly reduced the frequency of NVP among healthy pregnant women in Karang Indah, Indonesia¹¹⁷. Additionally, the consumption of ginger honey biscuits has been proven to decrease the intensity of NVP among teenage pregnancies in Jakarta, Indonesia¹¹⁸. Ginger in general contains antiemetic properties, which can improve gastric emptying and alleviate the symptoms of gastrointestinal disorders such as nausea, dyspepsia, and abdominal pain¹¹⁹. On the other hand, honey contains an abundant amount of vitamins and antibacterial properties that can also reduce the symptoms of nausea and vomiting¹²⁰. Therefore, these findings suggest that the combination of honey with ginger could lower the severity of NVP and provide a similar effect to vitamin B6 consumption. Besides the production of HCG, the other cause of NVP is *H. pylori* infections¹²¹. Although studies about the role of Malaysian honey in treating NVP are yet to be identified, KH has been established to possess antibacterial and antiulcer properties that can counteract the effects of *H. pylori* infections¹². Abdulrahman *et al.*¹²², also reported that Malaysian stingless bee honey is rich in hydrophilic vitamins such as B1, B3, and B6, which can alternatively be used as a supplement to reduce NVP symptoms.

Apart from NVP, iron deficiency anaemia (IDA) is well-recognised as the primary cause of anaemia in

pregnant women, as indicated by numerous studies¹²³. Anaemia in pregnancy is defined as a condition where maternal haemoglobin falls below 11g/dL (WHO, 2011). This condition normally occurs at the beginning of the second trimester when the foetal growth accelerates and there is a higher need for iron due to the increasing levels of foeto-placental demand¹²⁴. Nonetheless, a lack of essential nutrients such as those found in green vegetables, red meat, cereal, and bread also contributes to the occurrence of IDA¹²⁵. TH and GH have been reported to contain a substantial quantity of iron, ranging from 11.17 to 128.13 mg/kg and 8.45 to 142.37mg/kg, respectively⁴⁷. Besides that, KH and AH also contain variable amounts of iron, varying from 10.90 to 12.89 mg/kg. For that reason, TH, GH, KH, and AH can be regarded as alternative iron supplements to compensate for iron loss during pregnancy.

Folic acid deficiency is a common occurrence among pregnant women. Similar to iron, the demand for folate (vitamin B9) increases as the foetus grows and organ development progresses¹²⁶. Folate deficiency has been strongly associated with anaemia and congenital abnormalities¹²⁷. Folic acid deficiency may arise from multiple causes, including low dietary intake¹²⁸. Malaysian honeys such as TH, GH, and AH have been scientifically proven to contain folic acid as one of their bioactive compounds. In comparison with TH and GH, AH has been shown to have a significant amount of folic acid¹²⁹. This amount was reported to be higher than the Italian AH¹³⁰. Due to the high content of folic acid, it is advisable to consume AH during the early stage of conception, along with grain-based products such as cereal, pasta, and flour¹³¹. Furthermore, consumption of folic acid around the time of conception is strongly believed to have a prominent effect on the prevention of neural tube defects¹³². Since folate is an essential nutrient for DNA replication, its deficiency can impair folic acid metabolism, resulting in the development of neural tube defects¹³³. In addition to the nutritional needs, pregnant mothers experience physical and functional changes towards the end of pregnancy to prepare the fetus for delivery. However, if the mother is unable to adapt to the change, a range of difficulties may arise, potentially endangering both the foetus and the mother.

The most common complication that occurs towards the end of pregnancy, with a prevalence of approximately 2 to 15% is pre-eclampsia¹³⁴. Pre-

eclampsia is characterised by gestational hypertension that occurs after 20 weeks of pregnancy with coexisting proteinuria and certain types of organ damage. It can lead to substantial foetal and maternal morbidity and mortality¹³⁵. In the pathogenesis of pre-eclampsia, soluble fms-like tyrosine kinase 1 (sFlt1) plays an important role in producing an anti-angiogenic effect¹³⁶. sFlt1 binds to the vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) to block their angiogenic effect in order to prevent a rise in blood pressure¹³⁷. Therefore, an excess level of sFlt1 is strongly correlated with the pathogenesis of pre-eclampsia¹³⁸ and the administration of traditional Indonesian honey has been shown to suppress the sFlt1 bond, decrease blood pressure, and improve endothelial dysfunction in preeclampsia-induced rats¹³⁹. Furthermore, KH has the ability to reduce blood pressure due to its antioxidant properties. A consumption of KH at 1g/kg/day was proven to upregulate the Nrf2 mRNA protein expression and activate the catalase and glutathione-S-transferase enzymes which are essential to neutralise the reactive oxygen species in the kidney and ultimately normalise the blood pressure¹⁴⁰. Thus, the consumption of honey could be suggested as a preventative measure for pre-eclampsia.

Another complication that might occur due to physiological changes during pregnancy is urinary tract infection (UTI). The prevalence of UTI during pregnancy varies ranging from 32% to 64% and increases towards final stage of pregnancy¹⁴¹. Even though the etiological factor of gestational UTI is not fully understood, hormonal changes are believed to be associated with the occurrence of UTI¹⁴². Progesterone level during pregnancy progressively increases to a maximum plateau at 36 to 40 weeks¹⁰⁸. While elevated progesterone level has various advantages, it can also lead to a decrease in the bladder and ureteral tone¹⁴¹. Hormonal changes during pregnancy also affect the vaginal flora, which potentially facilitates the colonisation of uropathogens. The uropathogen that commonly causes UTI in pregnant women is *E. coli*¹⁴³. In general, UTIs during pregnancy can be treated with antibiotics that are safe for both the mother and foetus¹⁴⁴. Amoxicillin is one of the safest antibiotics available. Nonetheless, *E. coli* has developed high resistance to it¹⁴⁵. Uniquely, Malaysian honeys are proven to possess antibacterial properties against *E. coli* infections. A comparative study was conducted

among TH, AH, GH, and PH to compare their antibacterial activities against *E. coli*. Results obtained demonstrated that PH and AH have the highest MIC activities against *E. coli*, with the range of 25% followed by TH at 20% and GH at 12.5% respectively¹²⁰.

Besides, an *E. coli* study has reported that honey is effective against 60 different types of bacterial species, including Gram-positive and negative bacteria¹⁴⁶. The antibacterial property in honey is attributed to its osmolarity, acidity, and enzymatic reactions¹⁴⁷. During pregnancy, a mother is prone to infections due to changes in the immune system. In addition to UTIs, pregnant women are more susceptible to infections due to alterations in their immune systems. Other infections that can arise during pregnancy include group B streptococcus (GBS) and bacterial vaginosis (BV)¹⁴⁸. Both infections can be exposed transplacentally and cause serious complications for the foetus. TH and KH have demonstrated antibacterial activity against a wide range of bacteria that could make them a potential alternative to antibiotics for treating GBS and BV. Although more targeted research is required, the study shows that consumption of honey during pregnancy is effective against various bacterial infections.

The mother's ability to fight bacterial infection may be impaired due to physiological modifications to the immune system, including a reduction in cell-mediated immunity. Chronic bacterial infections may cause persistent inflammation and the development of various chronic complications⁴⁸. It has been reported that Malaysian honeys possess strong immunomodulatory properties that can significantly enhance the regulation of the immune system. The immunomodulatory mechanism works either by downregulating inflammatory factors and inflammatory cytokines or by stimulating inflammatory mediators to strengthen the anti-inflammatory mechanism within the body¹⁴⁹. Therefore, these findings suggest that the anti-inflammatory properties of Malaysian honeys could be employed to prevent persistent bacterial infections and alleviate the adverse effects of antibiotic resistance.

Weight gain during pregnancy is a natural and essential physiological process experienced by the mother to support foetal growth and development. Throughout pregnancy, women experience considerable increases in body weight, reflecting their nutritional status¹⁵⁰. However, if the weight exceeds 95 kg between 24 and 32 weeks of gestation, it is

more likely to cause insulin resistance with the tendency to develop gestational diabetes mellitus (GDM)¹⁵¹. GDM is a medical disorder characterised by glucose intolerance during pregnancy. It is associated with adverse maternal and neonatal outcomes such as macrosomia, which refers to the condition where the infant is larger than the typical size for their gestational age (LGA) at birth¹⁵². This incident can be prevented by controlling the weight gain from being excessive throughout the entire gestation period¹⁵³. Both nutritional therapy and exercise interventions are recommended to address this issue¹⁵⁰. Nevertheless, there is no consistent conclusion regarding the benefit of weight control during pregnancy. Honey has long been regarded as the best remedy for weight loss (Molan).

Previous research conducted by¹⁵⁴ unveiled that the consumption of natural honey was proven to lower the plasma glucose level among insulin-resistant patients. Possible mechanisms have been proposed to explain how honey regulates blood glucose levels. Fructose has been suggested to have a role in this process¹⁵⁵. Fructose stimulates glucokinase activity, which plays a crucial role in phosphorylating glucose to glucose 6-phosphate and is further metabolised to produce ATP¹⁵⁶. Since ATP is necessary for the secretion of insulin, preserved glucokinase activity is essential to maintain normal insulin secretion by pancreatic β -cells¹⁵⁷. The fructose levels in local TH, GH, AH, and PH have been shown to vary, ranging from 20.7 g to 26.8g, with GH exhibiting the highest content¹⁵⁸. Therefore, consuming Malaysian honey may serve as an alternative way to reduce the tendency to develop GDM with very limited amounts. In addition to fructose, another potential mechanism for the hypoglycemic effect of honey is believed to be attributed to the antioxidant properties¹⁵⁹. Normally, insulin is produced by β -cells of the pancreas in response to glucose synthesis. Evidence indicates that free radicals and oxidative stress substantially contribute to the pathogenesis of diabetes mellitus¹⁶⁰. The formation of free radicals increases lipid peroxidation activities, resulting in the development of insulin resistance due to oxidative stress¹⁶¹. In general, mitochondrial oxidative stress is the main source of insulin resistance in patients. Mitochondria reduce oxygen to water, and the remaining oxygen is transformed into free radicals, an important type of reactive oxygen species (ROS)¹⁶². In response to the

insulin signals, ROS either exerts a full physiological effect or transmits a negative signal to the insulin signalling pathway, which further develops into insulin resistance¹⁶³. Nonetheless, the antioxidant properties present in honey may have the ability to neutralise free radicals and protect the pancreas from oxidative stress.

A combination treatment of TH with antidiabetic therapy (metformin and glibenclamide) enhances the effectiveness of this therapy in reducing serum glucose and fructosamine levels in diabetic-induced rats, as compared to metformin and glibenclamide alone¹⁵⁵. Furthermore, a study conducted by¹⁶⁴ discovered that AH has a better effect on lowering blood glucose levels compared to manuka honey, as it has a lower glycaemic index. Generally, almost all types of Malaysian honey are known to have a lower glycemic index, which aids in the regulation of blood glucose levels¹⁶⁵. Honey also contains different types of minerals that play an important role in the maintenance of glucose intolerance and insulin production by the pancreatic β -cells¹⁶⁶. Additionally, honey contains a small amount of copper and zinc, which are also known to be involved in glucose and insulin metabolism¹⁶⁷. Although the mineral content present in honey is relatively small, daily consumption of TH for four weeks has been shown to elicit a pharmacological response that contributes to its hypoglycemic effect¹⁶³. Therefore, these findings suggest that the consumption of Malaysian honeys exerts a significant impact on the management of insulin resistance as a prevention for GDM.

Conclusion and future directions

In conclusion, this review suggests that Malaysian honeys such as TH, GH, PH, KH, and AH contain a variety of bioactive compounds to produce different types of biological properties that benefit human health. This includes possessing positive impacts towards the female reproductive system, mainly on the hormonal regulations, to improve fertility. Furthermore, the phenolic acid, vitamins, minerals, and antioxidant properties in Malaysian honeys can alternatively be used as a supplemental diet during pregnancy to prevent pre-term birth, NVP, pre-eclampsia, neural tube defects, and GDM. Malaysian honeys also contain antibacterial properties that can significantly reduce the risk of bacterial infection, causing UTIs in women. However, there is limited data available on the effects of Malaysian honeys on the reproductive system and pregnancy, which mostly

relies on preclinical studies only. There is also a lack of clinical trials, as well as a lack of standardisation of honey compositions (due to different geographical/botanical origins), which makes it difficult to compare results across studies.

Conflicts of Interest

The authors declare no conflict of interest.

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