



## The Role of Honey in Reproductive Age Gynecological Diseases: An Overview of Clinical Trials

Masoumeh Norouzi Allahleh Korabi<sup>1</sup>, Maedeh Rezghi<sup>2,3\*</sup>

<sup>1</sup>Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

<sup>3</sup>Department of History of Medical Sciences, School of Persian Medicine, Babol University of Medical Sciences, Babol, Iran

Received: 14 May 2023

Revised: 10 Oct 2023

Accepted: 25 Oct 2023

### Abstract

Honey has been used since ancient times to treat various diseases such as gynecological diseases. The current study aims to investigate clinical trials related to the therapeutic effects of honey on women's diseases. Databases including Web of Science, Scopus, PubMed, Google scholar, and SID were investigated for clinical studies focusing on honey in gynecological diseases up to 31 June 2022. Eligibility was checked based on selection criteria. Twenty-five clinical trials met the inclusion criteria. Therapeutic properties of honey and its compounds as a systemic and/or local treatment on vulvovaginal candidiasis, cervicitis, dysmenorrhea, premenstrual syndrome, labor pain, episiotomy and cesarean wounds, nipple fissure, breast cancer and intrauterine insemination (IUI), with the mechanisms of action of antibacterial, antifungal, anti-inflammatory, wound healing, analgesic, antioxidant and anticancer activities have been proven. It was also found that phenolic compounds including flavonoids and phenolic acids are the main ones responsible for most of these therapeutic effects of honey. This study supports the healing properties of honey in gynecological diseases at reproductive age. Also, in the current studies, honey proved safe with minor adverse effects. Of course, to achieve definitive conclusions about the effectiveness and safety of honey, it is necessary to conduct more clinical trials with a larger sample size, appropriate intervention duration, and optimal doses in future studies.

**Keywords:** Honey; Women's health; Natural product; Phenolic compounds; Clinical trial

**doi** <http://doi.org/10.18502/tim.v9i1.15089>

**Citation:** Norouzi Allahleh Korabi M, Rezghi M. **The Role of Honey in Reproductive Age Gynecological Diseases: An Overview of Clinical Trials.** Trad Integr Med 2024;9(1):53-65. <http://doi.org/10.18502/tim.v9i1.15089>

\*Corresponding Author: Maedeh Rezghi

Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

E-mail: maedehrezghi@yahoo.com, m.rezghi@mubabol.ac.ir

Copyright © 2024 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (<https://creativecommons.org/licenses/by-nc/4.0/>). Noncommercial uses of the work are permitted, provided the original work is properly cited.



## Introduction

Natural products have been known as effective way to prevent and treat various diseases since ancient times. In the last years, the popularity of traditional and complementary medicine has increased dramatically around the world [1]. Honey as a sweet and flavorful natural product is obtained from the nectar of flowers collected by honeybees [2,3] and has been used by humans for centuries due to its numerous and extraordinary nutritional and medicinal properties [4].

It is widely prescribed as a precious medicine for various diseases including different gynecological problems in traditional medicine such as Persian medicine and Ayurveda [5-8].

Honey is a natural solution supersaturated with sugars, in which fructose and glucose monosaccharides are the most abundant. It also is a source of different biologically-active compounds, such as phenolic compounds, essential minerals, organic acids, free amino acids, enzymes, proteins and vitamins [5,9]. These honey compounds are very dependent on their plant origin, environmental conditions and type of bee species involved in honey production [9,10].

In various studies, honey has exhibited strong wound healing, antifungal, antibacterial, antiviral, immunomodulatory and estrogen regulatory effects [2, 5]. Research also has shown that honey is a powerful source of natural antioxidants and reduces the risk of cancer and inflammatory processes [2,11]

Most of the healing properties of honey are caused by the presence of phenolic compounds. Phenolic compounds are one of the most important groups of components found in plants, which are divided into flavonoids (flavones, flavanones, isoflavones, flavonols, flavanols and anthocyanidins) and non-flavonoids. The phenolic compounds of honey are flavonoids and phenolic acids, that are potential indicators of the plant origin of honey [9].

Women's health plays an important role in the health of the family and society. Honey is effective in maintaining reproductive health and helping to treat gynecological disorders such as vulvovaginal candidiasis infection that affects women's lives. Various clinical studies have investigated the functions of honey individually or in combination with other substances in women's diseases [12-17].

However, no reviews are currently available on these studies. This comprehensive review study was conducted with the aim of collecting information and highlighting the effects of honey on diseases of women of reproductive age.

## Methods

This study registered under the ethical code IR.MUBABOL.REC.1401.142 in the Ethics Committee of Babol University of Medical Sciences. Elec-

tronic databases, including Web of Science, Scopus, PubMed, Google scholar, and SID have queried with the keywords "honey" OR "honey bee" OR "propolis" OR "royal jelly" AND "female disease" OR "women's health" OR "gynecology" OR "mastalgia" OR "postpartum pain" OR "premenstrual syndrome" OR "vaginosis" OR "vulvovaginal candidiasis" OR "Polycystic ovary syndrome" OR "breast cancer" OR "IUI" OR "intrauterine insemination" OR "cesarean section" OR "uterine Cervicitis" OR "nipple" OR "areolae" OR "labor induction" OR "episiotomy" in the title and abstract up to 31 June 2022.

Only clinical studies with English and Persian full-texts on gynecological diseases of reproductive age were included in our study. According to exclusion criteria (animal, cellular and experimental studies, review, case reports, and case series), the articles were evaluated.

## Results

A summary of the principal data of the obtained studies including disease type/ indication, study design, sample size, dosage form, intervention/ control, frequency and duration, dose and result is shown in Table 1.

In addition, studies on the role of honey on women's diseases have been explained more as follows:

### *Honey in Genital Tract*

#### *Honey in Vulvovaginal candidiasis (VVC)*

Vulvovaginal candidiasis (VVC) is defined as vaginal inflammation that often involves the vulva and is caused by *Candida* yeast [38]. VVC occurs due to an imbalance in the normal vaginal microbiota. VVC leads to vaginal erythema, itching, irritation, edema, dyspareunia and leucorrhea [39,40]. The treatment of choice for VVC is an azole antifungal drug, such as Clotrimazole. The inappropriate use of these antifungal drugs has led to drug resistance and, subsequently, greater prevalence of this infection [41,42]. In studies, resistance to clotrimazole has been reported [41].

On the other hand, honey has significant antimicrobial and anti-inflammatory activities. The studies have reported the efficacy of honey for the treatment of VVC both in vitro and in vivo [43,44]. Also, probiotics are helpful in maintaining and restoring the normal microbiota of the vagina for the treatment of VVC [45]. Honey contains oligosaccharides that promote the probiotic effect [46].

Banaeian et al. investigated the effects of vaginal cream of honey (combined the honey and a neutral cream in a 70:30 ratio) and vaginal cream of Clotrimazole (1%) in the treatment of VVC which resulted in no remarkable difference in the intensity of irritation (by using visual analog scale) and satisfaction with treatment between the two groups [13]. Additionally,

**Table 1.** Clinical trial studies of honey in gynecological diseases

Disease type/ Indication	Study design	Sample Size	Dosage form	Intervention/ control	Dose	frequency and duration	Result	Reference
Vulvovaginal candidiasis	Randomized, double blind, controlled clinical trial	80	Vaginal cream	Intervention: honey cream Control: Clotrimazole 1%	5 g mixture of honey and a neutral cream (in a ratio of 70:30) per night	1 week	No significant difference in inflammation, vaginal discharge, and irritation	[13]
Vulvovaginal candidiasis	Randomized, single-blind, controlled clinical trial	106	Vaginal gel	Intervention: honey gel Control: Clotrimazole 1%	5 g of 50% honey gel per night	1 week	No significant difference between the groups	[18]
Vulvovaginal candidiasis	Randomized, triple-blind, controlled clinical trial	70	Vaginal cream	Intervention: yogurt and honey gel Control: Clotrimazole 1%	5 g of yogurt and honey gel per night	1 week	↓Symptoms of Vulvovaginal candidiasis	[19]
Vulvovaginal candidiasis	Non-randomized comparative study	198	Vaginal cream	Intervention: yogurt and honey Control: tioconazole 100 mg vaginal tablet once daily for 7 days.	5 g honey and yogurt mixture vaginally twice daily	1 week	↓Symptoms of Vulvovaginal candidiasis	[20]
Vulvovaginal candidiasis	Triple blind clinical trial	105	Vaginal cream	Intervention 1: yogurt and honey Intervention 2: honey Control: clotrimazole	5 g vaginally daily	1 week	↓Symptoms of Vulvovaginal candidiasis	[21]
Vulvovaginal candidiasis	Triple blind clinical trial	100	Vaginal cream	Intervention: (honey- cinnamon vaginal cream) Control: clotrimazole	Honey 30%-cinnamon 3% vaginal cream	1 week	↓Burning ↓Symptoms of Vulvovaginal candidiasis	[22]
Vulvovaginal candidiasis	Double blind clinical trial	75	Vaginal cream	Intervention 1: honey vaginal cream Intervention 2: honey and clotrimazole vaginal tablet Control: clotrimazole 100 mg vaginal tablet	5 g vaginally daily	1 week	↓Symptoms of Vulvovaginal candidiasis	[23]
Vulvovaginal candidiasis	Singleblind randomized controlled clinical	120	Vaginal cream	Intervention: honey- olive oil vaginal cream Control: clotrimazole	5 g vaginally daily	1 week	No significant difference	[24]

Cervicitis	Quasi-experimental, clinical trial	70	Vaginal cream	Intervention: crem vaginal Flixweed- Honey	Honey 50%	2 weeks	↓Fragility in contact with swab ↓Tenderness ↓Wound size and depth	[14]
Labor	Randomized controlled clinical	70	Syrup	Intervention: honey syrup and activity with birth ball Control: routine care	2/5 tablespoons of syrup in 150 mL of water per 30-60 min	Active phase labor	↓Labor pain	[25]
Labor	Double blind control clinical trial	87	Syrup	Intervention 1: 750 mg saffron and 75 g honey in 450 mL of water Intervention 2: 750 mg saffron and 15 g sodium saccharin in 450 mL of water control group: containing 15 g sodium saccharin plus saffron food coloring in 450 mL of water	150 mL of the syrup at the onset of the active phase of labor and 150 mL of the syrup was repeated every two hours up to 3 times during the labor	Active phase labor	↑Progress of labor	[26]
Labor	Double blind control clinical trial	90	Syrup	Intervention 1: honey plus date Intervention 2: placebo Control: routine care	92 g date-honey plus 140 mL water in the first active phase then 40 g date-honey plus 600 mL water	Phase labor	↑Progress of labor ↓Labor duration	[27]
Dysmenorrhea	Single-blind crossover	60	Oral	Intervention: pure honey then impure honey Control: impure honey then pure honey	40 g every other day	3 cycles	↓Severity of pain ↓Bleeding	[28]
Dysmenorrhea	A randomized cross over	56	Oral	Intervention: honey Control: mefenamic acid	1.2 mg/kg honey	2 consecutive months	No significant differences	[15]
Dysmenorrhea	Single-blind cross over	60	Oral	Intervention: pure honey Control: impure honey	5 teaspoons (40 g)/ Every other day	2 cycles	↓Headache ↓Nausea ↓Vomiting	[29]
Premenstrual syndrome	Triple blind clinical trial	110	Capsule	Intervention: Royal jelly placebo: paraffin	1000 mg daily	2 cycles	↓PMS score	[30]
Episiotomy	A doubleblind randomized clinical trial	120	Cream	Intervention 1: honey Intervention 2: curcumin placebo cream	The entire wound was covered by honey twice a day	10 successive days after birth	↑Wound healing ↓Pain intensity.	[31]

Episiotomy	Double-blind three-group randomized trial	120	Cream	Intervention1: honey Intervention2: phenytoin cream 1 % placebo cream	Honey cream 30 % every night	10 nights	↑Wound healing	[16]
Cesarean Section	Triple blind randomized clinical trial	88	Gel	Intervention1: honey gel placebo: free-honey gel	25% honey twice a day	2 weeks	↓Redness ↓Edema ↓Hematoma ↑Wound healing	[32]
Cesarean Section	Triple blind clinical trial	146	Gel	Intervention: honey gel Placebo: gel without honey	25% honey twice a day	2 weeks	↓Cesarean wound pain ↓ Need for analgesics	[33]
Cesarean Section	Prospective Randomized controlled clinical trial	132	Topical	Intervention: honey placebo: FD&C Yellow No. 6, distilled water, polyvinylpyrrolidone, tri ethanol amine and Carbopol 940. Control: no intervention	The entire wound was covered, twice a day	16 consecutive days post caesarean	↑Wound healing	[34]
Breast Cancer	Clinical trial before and after intervention	119	Oral	Intervention: honey and cinnamon	A tablespoon of honey (30 g) and a teaspoon of cinnamon (4 g)/ 3times daily	1 week	↑Quality of life	[35]
Breast Cancer	Double-blind clinical trial	50	Capsule	Intervention: Propolis honey Control: Starch powder	250 mg Propolis honey/ twice a day	3 months	↓TNF- $\alpha$ , IL-2, PAB	[36]
Nipple fissure	Clinical trial	150	Topical	Intervention 1: Honey Intervention 2: Yarrow; 30 g twice a day Control: breast milk; a few drops of milk on their breast twice a day	topical twice a day after finishing the breast-feeding	1 week	↓Severity fissure	[17]
IUI	Non-randomized clinical trial study	447	Vaginal cream	Intervention: Mace and honey	100 g of honey with 1 g of Mace	The 7th day of menstruation until the day before performing IUI	↑Pregnancy rate	[37]

Seifinadergoli et al. (2018) compared the effects of honey gel (50%) and clotrimazole vaginal cream 1% in the treatment of VVC symptoms. They reported the noticeable effect of honey in the treatment of vaginal candidiasis. After treatment, no significant difference was observed between the groups [18].

In 2009, in a clinical trial, Fazel et al. administered vaginal clotrimazole and vaginal honey for 7 days to VVC patients. Honey alone or in combination with clotrimazole was more effective in treating VVC than clotrimazole alone [23].

In 2015, Darvishi et al. and in 2021, Jahdi et al. proved

that yogurt and honey vaginal cream is significantly more effective than clotrimazole cream in improving some symptoms of vaginal candidiasis [19,21].

Also, Abdulmonem et al. (2012) compared and evaluated a honey and yogurt mixture with tioconazole for the treatment of VVC in pregnancy. The intervention group received 30 g of a mixture of honey and yogurt vaginally, and the control group received 100 mg of tioconazole vaginal tablets for 7 days. The results showed that in the intervention group, the rate of clinical improvement was remarkably higher than the control group [20].

Furthermore, Parsapour et al. (2018) evaluated the effect of clotrimazole and Nika vaginal creams on VVC treatment. Nika vaginal cream contains honey, propolis and olive oil. Clotrimazole cream and Nika cream showed the same effects in the treatment of VVC [24]. Rasouli et al. (2019) investigated the effect of vaginal cream of honey (30%) and cinnamon (3%) on VVC improvement. Honey and cinnamon vaginal cream was meaningfully irritating less than clotrimazole, but the culture results were similar in the two groups [22].

### Honey in Cervicitis

The inflammation of the cervix by an infectious agent is named Cervicitis and approximately 50% of all cases of cervicitis are caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis* [47].

In a quasi-experimental study, 72 patients underwent vaginal honey and flixweed formulation treatment for two weeks. Honey and water were mixed and heated until the added water evaporated. After that, honey was mixed with crushed flixweed seeds in a ratio of 1:2 and then flixweed- honey was packed in 50 g tubes and used for two weeks. Patients were asked to rate their symptoms of discharge, irritation, itching, pain during intercourse, and post-intercourse bleeding on a scale of 0 to 10 before and after taking the medication in accordance with the visual analog scale. The results proved that the vaginal formulation of honey and flixweed notably improves cervicitis clinical symptoms [14].

### Honey in Delivery

The pain of childbirth can be severe and the anxiety, stress and fear of the pregnant woman increase its intensity [48].

Taavoni et al. evaluated the effect of honey syrup consumption (two and a half tablespoons of honey in 150 mL of water) and special pelvic movements by birth ball on the severity of childbirth pain in primiparous women. During the active stage of labor, mothers consumed the syrup every half to one hour, and did pelvic tilt movements with the birth balls. Honey syrup was effective in reducing labor pains in nulliparous women [25]. In another study, saffron and honey syrup

shortened the duration of stages of labor in nulliparous women [26]. Kordi et al. (2010) have shown a high rate of normal labor in honey and date syrup group, also the length of delivery in the honey-date syrup group was shorter than the other two groups including the placebo group and the usual care group [27]. The analgesic effect of honey may be due to the reduced accumulation of prostaglandin in the blood [29].

### Honey in Dysmenorrhea

Dysmenorrhea is one of the foremost common causes of pelvic pain. It adversely affects patients' quality of life and sometimes causes activity restriction [49]. Dysmenorrhea pain can be caused by excessive secretion of prostaglandins and enhancement of uterine contractions [50]. Nonsteroidal anti-inflammatory drugs, oral contraceptives, and depo-medroxyprogesterone acetate are therapy of choice in women with primary dysmenorrhea which cause complications for patients. On the other hand, there is some evidence of benefits with the use of topical heat, herbal remedies, and complementary medicine [51].

Mirbagher et al. (2012) indicated that the use of pure honey in women reduces the intensity of pain and bleeding [28]. In 2013, another study by Mirbagher et al. evaluated the role of pure and impure honey on headache, nausea and vomiting in women with dysmenorrhea. The severity of nausea, vomiting and headache caused by dysmenorrhea was significantly reduced after consuming pure honey [29]. In 2017, Farahani et al. have shown honey capsule and mefenamic acid capsule cause the same amount of pain relief in women with primary dysmenorrhea [15]. Al-Waili and Boni demonstrated that honey may lead to a decrease in levels of prostaglandin in normal individuals [52]. Honey can reduce the concentration of thromboxane B2 and Prostaglandin E2 and alpha2 in the blood; thus, it may be able to decrease menstrual pain [28].

### Honey in Premenstrual Syndrome (PMS)

In 2014, Taavoni et al. showed that royal jelly was significantly effective in the decrease of PMS. In this study, the effect of royal jelly 1000 mg capsule and placebo capsule was orally assessed on 110 medical sciences students with PMS. The study has shown that taking 2 months of royal jelly was remarkably effective in the reducing PMS [30].

### Honey in Episiotomy and Cesarean Section Wounds

Honey has been widely used for healing wounds for centuries, and today its use has been expanded due to its antimicrobial properties [53,54]. Honey accelerates the healing process through its acidity, high osmolality and antibacterial activity [53].

Studies have shown that in patients suffering from wound infection after cesarean section or hysterectomy



tomy, local use of honey accelerates the healing of microbial infections, minimal scarring formation, decreases antibiotic consumption, and hospitalization [55]. Lavaf et al. investigated the effect of honey cream, phenytoin cream and placebo on the severity of episiotomy pain in 120 nulliparous women. On the 1st, 7th, and 14th days after delivery, pain intensity scores did not indicate significant differences between the three groups, but according to the results, honey showed stronger wound healing activity than phenytoin [16]. A randomized controlled trial study by Nikpour et al. (2019) assessed the effect of honey cream and curcumin cream on episiotomy wound healing and pain in 120 women. In this study, honey, curcumin and placebo creams were applied twice a day for 10 consecutive days after birth on the episiotomy wound. Honey and curcumin creams showed approximately the same effects on pain severity and episiotomy wound healing [31]. In another study in 2013 by Shirvani et al., mothers were randomly divided into intervention (honey gel), placebo (gel without honey) and control (no intervention) groups. The subjects of the intervention and placebo groups were asked to apply the gel twice a day for 14 days on the cesarean wound. The concentration of honey in the gel of the intervention group was 25%. There was a remarkable difference between the three groups in terms of pain intensity on the 7th and 14th days after delivery, and honey was significantly effective [33].

Heydari et al. (2013) randomly divided the participants into three intervention (honey), placebo (local disinfectant) and control (no intervention or placebo) groups. Although, there was no significant difference between the groups in the pain intensity and the mean REEDA score (Redness, Edema, Ecchymosis, Discharge from the wound and Approximation of the perineal tissues) at 10 days after cesarean section. However, in the mean REEDA score 40 days after cesarean section, a statistically significant difference was observed between the honey and control groups, as well as the placebo and control groups, although there was no significant difference between the honey and placebo groups [34].

Also, there are limited and contradictory studies on the effects of honey and phenytoin in reducing pain resulting from episiotomy and cesarean section wounds [56,57]. In a study by Nikpour et al., women in the intervention group received 25% honey gel and the placebo group received honey-free gel topically twice a day for 14 days to heal cesarean wounds. The results showed that honey was notably effective in healing wounds caused by cesarean section [32].

### *Honey in Breast*

#### **Breast Cancer**

Breast cancer in women is the most common malignant tumor and the second most common cause of cancer-related death. Various genetic and environmental factors are involved in this disease [58-60].

In 2017, Aghamohammadi et al. proved that the use of a mixture of 30 g honey and 4 g cinnamon powder, three times daily for 1 week in patients with breast cancer improves most of the criteria related to the quality of life [35]. In 2020, Darvishi assessed the effect of propolis consumption (250 mg/ twice daily which started a week prior to chemotherapy) in women with breast cancer undergoing chemotherapy. Propolis has shown a decrease in tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-2 and PAB markers and, as a result, antioxidant and anti-inflammatory properties in the intervention group compared to the placebo group [36].

### **Honey in Nipple Fissure**

The breast fissure is a very common skin lesion on the tip and areola of the breast, which is reported in 80-90% of lactating women. The most common causes of breast fissures include incorrect breastfeeding and improper nipple sucking [61]. These nipples are often infected with bacteria, candida or other microorganisms [62].

Among the effective therapies for nipple fissure is the use of herbal medicines and complementary medicine. Firouzabadi et al. evaluated the effects of honey, yarrow and breast milk on the healing of nipple fissure in lactating women. The results showed a remarkable decrease in the severity of nipple fissure in all three groups and there was no significant difference between the three groups [17].

### *Honey in Intrauterine Insemination (IUI)*

Intrauterine insemination (IUI) is one of the oldest and most effective assisted reproductive methods for couples who have infertility for various reasons [63,64]. In a non-randomized clinical trial, Kavousi et al. divided infertile women into two intervention and control groups.

Women in both groups received clomiphene or letrozole from the 3rd to the 7th day of menstruation and human menopausal gonadotropin (HMG) on the 6th 7th and 8th days. IUI was performed 36 hours after HCG injection. In the intervention group, in addition to the above treatments, natural formulation containing honey was used from the seventh day of menstruation until the day before performing IUI. In this study, the pregnancy rate was higher in the group receiving the formulation containing honey, but this difference was not significant [37]. It has also been found that vaginal use of honey may affect the natural flora of the vagina and increase sperm motility [65].

### Potential Side Effects

In most of the studies, no side effects were reported and honey is relatively safe and free of adverse effects. The application of honey topically may provide a brief stinging sensation in some patients. But in general, it is described as an analgesic, anti-inflammatory and wound-healing dressing, non-irritating. Although allergies to honey are rare, pollen or bee protein might cause allergic reactions in susceptible individuals. Excessive use of honey could cause tissues dehydration. Also, using large amounts of honey may raise blood glucose levels in diabetic patients. Since honey contains sugar, it should be consumed in moderation. During production, honey may become contaminated with pathogens. Although rare, some infants have contracted botulism after consuming honey orally. Therefore, it is recommended not to be used honey in children under 12 months [10,66].

### Discussion

Gynecological disorders such as dysmenorrhea, premenstrual syndrome, abortion, menstrual disorders, infertility and delivery problem are among the most common reasons for women of reproductive age to visit health centers [6]. Lack of adequate therapeutic response with conventional treatments, as well as concerns about side effects of current medicines, encourage patients to use natural products and traditional medicine [67].

This study was designed to review the efficacy of honey as a natural product in women's diseases of reproductive age. In this comprehensive review, we found relevant clinical trials that evaluated the effect of honey alone and in combination with other ingredients on women's diseases such as VVC, cervicitis, delivery problems, dysmenorrhea, PMS, episiotomy and cesarean section wounds, IUI, and breast disorders (breast Cancer, nipple fissure).

Honey in these studies was prescribed through oral and/or topical routes of administration as different formulations like syrup, capsule, vaginal cream, topical cream, and gel.

In cases of infection and inflammation like vulvovaginal candidiasis and cervicitis, as well as in cases of the wound like nipple fissure, episiotomy and cesarean section, topical honey was significantly effective and safe. Also, oral administration of honey in the improvement of breast cancer, dysmenorrhea, PMS and labor problems was well-tolerated by patients without any notable side effects. Therefore, according to the findings, oral and topical administration of honey can be a safe adjuvant treatment for the healing of different women's diseases.

Various trials and in vitro studies have shown the antibacterial properties of honey on both Gram-positive and Gram-negative bacteria [68]. Honey inhib-

its the growth of pathogenic strains like *Escherichia coli*, *Helicobacter pylori*, *Staphylococcus aureus* and *Streptococcus pyogenes*. Also, it reduced the growth of infecting strains in wounds like *Acinetobacter baumannii*, *Proteus* spp., *Klebsiella pneumonia* and *Pseudomonas aeruginosa* [69].

Honey antibacterial activity is due to various factors such as low pH, high osmotic pressure, low protein content, as well as production of hydrogen peroxide by glucose oxidase enzyme, methylglyoxal and defensin-1 (antimicrobial peptide) [70]. In addition, its high sugar content can be beneficial in inhibiting bacteria through osmosis [71]. Also, some non-peroxide substances like flavonoids, phenolic acids, and lysozyme in honey have a strong antibacterial role [72,73].

One of the activities related to antibacterial properties is wound healing, which is one of the most studied and effective uses of honey [74]. Most of the wounds such as bed sores, burns, diabetic, cracked nipples, fistulas, amputation, cervical, varicose, traumatic and surgical wounds or abdominal wall and perineum wounds have been confirmed to be well treated with honey [10,66]. Honey dressing increases the speed of infection control, healing process and pain reduction [75]. Honey has a notable cleansing effect on wounds, stimulation of tissue regeneration, reduction of inflammation, edema and scar formation and effective wound debridement [10,55].

Studies have proven the antifungal effect of honey against various species of *Candida*, *Penicillium*, *Aspergillus*, *Malassezia* and *Saccharomyces* [76]. Its antifungal activity is due to high sugar contents, methylglyoxal and glucose oxidase [77]. The honey flavonoid content reduces fungal growth, alters membrane integrity and external morphology and restrains some cellular processes related to the growth of germ-tube. Also, studies have shown that honey flavonoids affect hyphal transmission by reducing the percentage of cells in G2/M and/or G0/G1 phases [78].

On the other hand, honey affects the growth of probiotic microorganisms. Probiotics modify the balance of intestinal microflora and stimulate the growth and activity of beneficial organisms and suppress harmful bacteria. Studies have shown the potential of honey to increase the growth of *Lactobacillus* and *Bifidobacterium*, mainly attributed to its high content of oligosaccharides [79].

The anti-inflammatory effect of honey has been demonstrated in cell culture, animal studies and clinical trials [80]. Honey has been found to remarkably reduce edema and suppress the expression of pro-inflammatory cytokines like TNF- $\alpha$ , NO, iNOs, IL-1, IL-6, IL-10, PGE2 and COX-2. Honey was also shown to decrease the translocation of NF- $\kappa$ B to the nucleus and prevent the destruction of I $\kappa$ B $\alpha$  [81,82]. Phenolic acids like caffeic acid, gallic acid and ellagic acid, as



well as flavonoids like quercetin, apigenin, catechins, galangin and rutin present in honey affect the activity of pro-inflammatory mediators such as COX-2, iNOs, MMP-9 and prostaglandins [83].

It is known that honey with different plant origins has a high antioxidant capacity. These antioxidant properties can prevent various acute and chronic diseases like inflammation and cancer [2,84,85]. Phenolic acids and flavonoids of honey are the main compounds responsible for its strong antioxidant activity. In addition, amino acids, proteins, sugars, organic acids, and carotenes in honey also play a role in antioxidant activity [86]. The mechanisms of antioxidant action of honey are related to the inhibition of free radicals, superoxide radical action, chelation of metal ions, hydrogen donation and flavonoid substrate function for hydroxyl [87]. The anticancer impact of honey has been proven in different studies both from the point of view of prevention and treatment [88]. Honey is effective in various stages of cancer, in its initiation, proliferation, and progression [89]. Several anticancer mechanisms for honey have been found in various studies, including induction of apoptosis, cell cycle arrest or antiproliferative activity, antioxidant properties and modulation of oxidative stress, improvement of inflammation, modulation of estrogen, antimutagenic, modulation of insulin, induction of MOMP, inhibition of angiogenesis and immunomodulatory effects [84]. Apoptosis is the process of programmed cell death to remove damaged cells, which plays a significant role in cancer prevention. Also, many common medicines prescribed to treat cancer induce apoptosis. Researchers have confirmed that honey is a good inducer of apoptosis in various types of cancer cells, especially cancers related to women such as breast and cervical cancer [90]. Honey induces apoptosis through its cytotoxic effect, which is mostly because of decrease in the mitochondrial membrane potential and the increase in the expression of pro-apoptotic proteins like caspase 3 and 9 [91]. It has also been determined that the impact of honey on breast cancer is due to its role in diminishing tumor growth and grade, estrogenic activity and its effect on some proteins of inflammatory pathways [92]. These properties of honey are attributed to the high tryptophan and phenolic contents (flavonoids and phenolic acid) [93].

Various animal and human researches on honey have also shown its anxiolytic, anticonvulsant, sedative and analgesic effects and it has been proved that these neuropharmacological effects are mainly related to the polyphenols present in honey [94]. Analgesic activities of different types of honey from different regions have been identified. In studies, participants who received honey orally had elevated pain thresholds. These antinociceptive effects are most likely mediated by opioid receptors [95]. Moreover, it has been

found that honey can decrease the concentration of prostaglandins of PGE2 and PGF 2 $\alpha$  as well as thromboxane B2 (TXB2) in the blood; therefore, its consumption can diminish menstrual pain in women [28]. As proved in various studies, honey has significant antibacterial, antifungal, wound healing, anti-inflammatory, antioxidant, anticancer and analgesic effects, and most of the therapeutic properties of honey reported by clinical studies in women's diseases such as VVC, cervicitis, breast cancer, nipple fissure, labor pain, dysmenorrhea, premenstrual syndrome, episiotomy and cesarean wounds are related to these medicinal effects (Figure 1). It has also been confirmed that phenolic compounds such as flavonoids and phenolic acids are the main active ingredients responsible for most of the therapeutic properties of honey.

The present review has three main limitations that should be addressed: (1) Some of the clinical trials were missing due to exclusion criteria, including those with their full-texts in languages other than English and Persian. (2) Animal, cellular and experimental studies have not been included. (3) The composition of honey is highly dependent on its plant origin, environmental conditions, and the type of bee species involved in honey production. The sources of honey production are varied in different studies, which has challenged accurate conclusions and comparisons. In addition, most of the studies do not mention the details of the source of honey. The probable differences in the outcomes of the studies may be linked to the source of the honey that is not specified in most studies. However, this study is the first review of the therapeutic effects of honey on women's diseases, and in this research, the possible mechanism of honey in each of these diseases is also discussed.

## Conclusion

Honey has been used for the treatment of various diseases such as gynecological disorders from ancient times. Current study supports the remarkable impacts of honey and its compounds individually or in combination with medicinal plants or other natural products on women's health with great tolerability and insignificant side effects. Studies showed that the medicinal effects of honey can be mainly due to its phenolic compounds. However, more studies are needed to evaluate the specific cellular and molecular mechanisms of the treatment effects of honey, alone or as adjuvant therapy.

## Conflict of Interests

Authors state no conflict of interest.

## Acknowledgements

None.

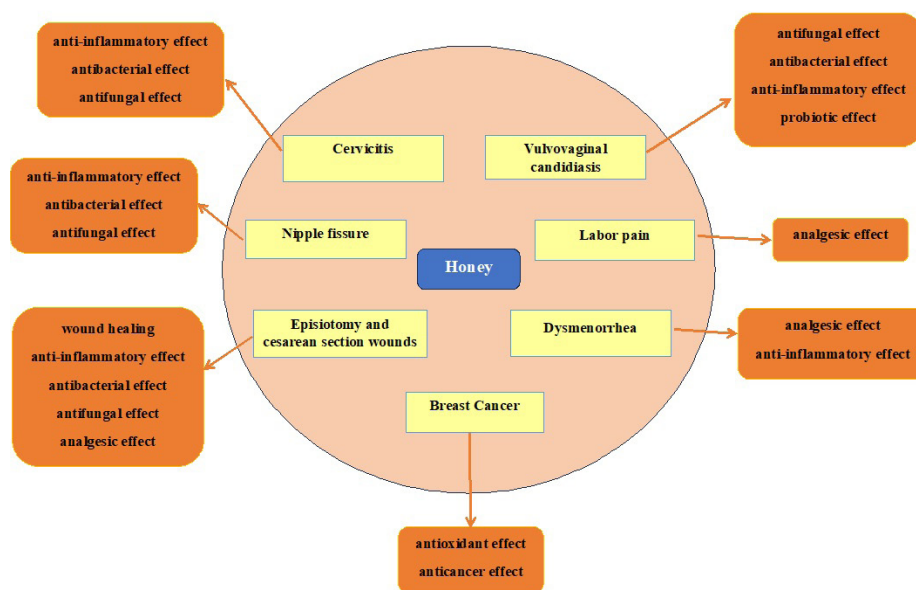


Figure 1. The mechanism of honey in the gynecological diseases

## References

- [1] Rezghi M, Choopani R, Fahimi S, Sheikholeslami MA, Hamzeloo-Moghadam M. Formulation of a traditional polyherbal product to a standard pharmaceutical syrup and development of its quality control methods. *Res J Pharmacogn.* 2019;6:53-59.
- [2] Ahmed S, Sulaiman SA, Baig AA, Ibrahim M, Liaqat S, et al. Honey as a potential natural antioxidant medicine: an insight into its molecular mechanisms of action. *Oxid Med Cell Longev* 2018;2018:8367846.
- [3] Topitzhofer E, Lucas H, Chakrabarti P, Breece C, Bryant V, et al. Assessment of pollen diversity available to honey bees (Hymenoptera: Apidae) in major cropping systems during pollination in the western United States. *J Econ Entomol* 2019;112:2040-2048.
- [4] Samarghandian S, Farkhondeh T, Samini F. Honey and health: A review of recent clinical research. *Pharmacogn Res* 2017;9:121-127.
- [5] Puscas A, Hosu A, Cimpoi C. Application of a newly developed and validated high-performance thin-layer chromatographic method to control honey adulteration. *J Chromatogr A* 2013;1272:132-135.
- [6] Balamurugan S, Vijayakumar S, Prabhu S, Yabesh JM. Traditional plants used for the treatment of gynaecological disorders in Vedaranyam taluk, South India-An ethnomedicinal survey. *J Tradit Complement Med* 2018;8:308-323.
- [7] Aziz MA, Khan AH, Ullah H, Adnan M, Hashem A, et al. Traditional phytomedicines for gynecological problems used by tribal communities of Mohmand Agency near the Pak-Afghan border area. *Rev Bras Farmacogn* 2018;28:503-511.
- [8] Sadeghi Z, Mahmood A. Ethno-gynecological knowledge of medicinal plants used by Baluch tribes, southeast of Baluchistan, Iran. *Rev Bras Farmacogn* 2014;24:706-715.
- [9] Cianciosi D, Forbes-Hernández TY, Afrin S, Gasparri M, Reboredo-Rodríguez P, et al. Phenolic compounds in honey and their associated health benefits: A review. *Molecules* 2018;23:2322-2342.
- [10] Eteraf-Oskouei T, Najafi M. Traditional and modern uses of natural honey in human diseases: a review. *Iran J Basic Med Sci* 2013;16:731-742.
- [11] Musa Özcan M, Al Juhaimi F. Honey as source of natural antioxidants. *J Apic Res* 2015;54:145-154.
- [12] Zaid SSM, Ruslee SS, Mokhtar MH. Protective roles of honey in reproductive health: a review. *Molecules* 2021;26:3322-3337.
- [13] Banaeian S, Sereshti M, Rafieian M, Farahbod F, Kheiri S. Comparison of vaginal ointment of honey and clotrimazole for treatment of vulvovaginal candidiasis: A random clinical trial. *J Mycol Med* 2017;27:494-500.
- [14] Nabimeybodi R, Meyari A, Vahiddastjerdi M, Hajimehdi-poor H, Ghasemi E, et al. The effect of flixweed-honey vaginal product on cervicitis: a clinical trial. *Res J Pharmacogn* 2018;5:41-49.
- [15] Farahani ĘLA, Hasanpoor-Azghdy SB, Kasraei H, Heidari T. Comparison of the effect of honey and mefenamic acid on the severity of pain in women with primary dysmenorrhea. *Arch Gynecol Obstet* 2017;296:277-283.
- [16] Lavaf M, Simbar M, Mojab F, Majd HA, Samimi M. Comparison of honey and phenytoin (PHT) cream effects on intensity of pain and episiotomy wound healing in nulliparous women. *J Complement Integr Med* 2018;15.
- [17] Firouzabadi M, Pourramezani N, Balvardi M. Comparing the effects of yarrow, honey, and breast milk for healing nipple fissure. *Iran J Nurs Midwifery Res* 2020;25:282-285.
- [18] Spence D. Candidiasis (vulvovaginal). *Clin Evid* 2010;01:815-854.
- [19] Mtibaa L, Fakhfakh N, Kallel A, Belhadj S, Salah NB, et al. Vulvovaginal candidiasis: Etiology, symptomatology and risk factors. *J Mycol Med* 2017;27:153-158.
- [20] Eckert L, Hawes S, Stevens C, Koutsky L, Eschenbach D, et al.

- Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynaecol* 1998;92:757-765.
- [21] Mendling W, Atef El Shazly M, Zhang L. Clotrimazole for vulvovaginal Candidosis: more than 45 years of clinical experience. *Pharmaceuticals* 2020;13:274-297.
- [22] Crowley P, Gallagher H. Clotrimazole as a pharmaceutical: past, present and future. *J Appl Microbiol* 2014;117:611-617.
- [23] Banaeian-Borujeni S, Mobini GR, Pourgheysari B, Validi M. Comparison of the effect of honey and miconazole against *Candida albicans* in vitro. *Adv Biomed Res* 2013;2:57-62.
- [24] Irish J, Carter DA, Shokohi T, Blair SE. Honey has an antifungal effect against *Candida* species. *Med Mycol* 2006;44:289-291.
- [25] Xie HY, Feng D, Wei DM, Mei L, Chen H, et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. *Cochrane Database Syst Rev* 2017;11:61.
- [26] Ismail NH, Ibrahim SF, Jaffar FHF, Mokhtar MH, Chin KY, et al. Augmentation of the female reproductive system using honey: a mini systematic review. *Molecules* 2021;26:649-666.
- [27] Seifinadergoli Z, Nahidi F, Safaiyan A, Javadzadeh Y, Eteraf-Oskouei T. Comparison of the efficacy of honey gel and clotrimazole cream in the treatment of vaginal candidiasis symptoms: a randomized clinical trial. *Electron Physician* 2018;10:6904-6911.
- [28] Fazel N, Hashemian M. The effect of honey on vulvovaginal candidiasis. *Int J Gynaecol Obstet* 2009;107:S563-S563.
- [29] Darvishi M, Jahdi F, Hamzegardeshi Z, Goodarzi S, Vahedi M. The Comparison of vaginal cream of mixing yogurt, honey and clotrimazole on symptoms of vaginal candidiasis. *Glob J Health Sci* 2015;7:108-116.
- [30] Jahdi F, Hamzegardeshi Z, Kuolaei MD, Vahedi M, Goodarzi S. Vulvovaginal candidiasis symptom reduction honey, yogurt-and-honey and clotrimazole vaginal cream--a triple blind randomized control trial. *J Evol Med Dent Sci* 2021;10:515-522.
- [31] Abdelmonem AM, Rasheed SM, Mohamed AS. Bee-honey and yogurt: a novel mixture for treating patients with vulvovaginal candidiasis during pregnancy. *Arch Gynecol Obstet* 2012;286:109-114.
- [32] Parsapour H, Masoumi SZ, Shayan A, Moradkhani S, Ghiasian SA, et al. Comparison of the effects of nika vaginal cream with clotrimazole cream on vaginal candidiasis symptoms: a randomized single-blind clinical trial. *Iran J Nurs Midwifery Res* 2021;26:521-525.
- [33] Rasooli T, Nahidi F, Mojab F, Nasiri M, Parsapour H. Effect of honey cinnamon vaginal cream and clotrimazole vaginal cream on improvement of candida vaginitis symptoms in women: randomized clinical trial. *Iran J Obstet Gynecol Infertil* 2019;22:59-67.
- [34] Hester EE, Middleman AB. A clinical conundrum: chronic cervicitis. *J Pediatr Adolesc Gynecol* 2019;32:342-344.
- [35] Smith CA, Collins CT, Crowther CA, Levett KM. Acupuncture or acupressure for pain management in labour. *Cochrane Database Syst Rev* 2011;7:CD009232.
- [36] Taavoni S, Nazem Ekbatani N, Haghani H. Co-effect of pelvic special moves by birth ball and consumption of honey syrup on the severity of labor pain in nulliparous women. *Complement Med J* 2018;7:2052-2062.
- [37] Ghaderi S, Zaheri F, Nouri B, Shahoei R. The Effect of Honey Saffron Syrup on Labor Progression in Nulliparous Women. *J Pharm Res Int* 2019;28:1-8.
- [38] Kordi M, Nasiri N, Safarian M, Esmaili H, Shadjuo K. The effect of oral honey-date syrup intake during labor on labor progress of nulliparous women. *Iran J Obstet Gynecol Infertil* 2010;13:23-30.
- [39] Mirbagher Ajorpaz N, Hafezi M, Salehi S, Tayebi A, Shenasa F, et al. Comparing the effect of pure and impure honey on severity of pain, amount of bleeding, and duration and interval of menstrual cycles in female students with primary dysmenorrhea. *Evid Based Care J* 2012;2:23-33.
- [40] Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. *Am Fam Physician* 2014;89:341-346.
- [41] Bernardi M, Lazzeri L, Perelli F, Reis FM, Petraglia F. Dysmenorrhea and related disorders. *F1000Res* 2017;6:1645-1652.
- [42] French L. Dysmenorrhea. *Am Fam Physician* 2005;71:285-291.
- [43] Mirbagher Ajorpaz N, Shahshahani M, Rahemi Z. The effect of pure and impure honey on Nausea, vomiting and headache of dysmenorrhea. *J Kerman Univ Medical Sci* 2013;16:510-517.
- [44] Al-Waili NS, Boni NS. Natural honey lowers plasma prostaglandin concentrations in normal individuals. *J Med Food* 2003;6:129-133.
- [45] Taavoni S, Barkhordari F, Goushegir A, Haghani H. Effect of royal jelly on premenstrual syndrome among iranian medical sciences students: a randomized, triple-blind, placebo-controlled study. *Complement Ther Med* 2014;22:601-606.
- [46] Molan PC, Rhodes T. Honey: a biologic wound dressing. *Wounds* 2015;27:141-151.
- [47] Saikaly SK, Khachemoune A. Honey and wound healing: an update. *Am J Clin Dermatol* 2017;18:237-251.
- [48] Al-Waili NS. Mixture of honey, beeswax and olive oil inhibits growth of *Staphylococcus aureus* and *Candida albicans*. *Arch Med Res* 2005;36:10-13.
- [49] Nikpour M, Delavar M, Khafri S, Ghanbarpour A, Moghadamnia A, et al. The use of honey and curcumin for episiotomy pain relief and wound healing: A three-group double-blind randomized clinical trial. *Nurs Midwifery Stud* 2019;8:64-69.
- [50] Shirvani MA, Nikpour M, Azadbakht M, Banihosseini SZ, Zanjani R. The effect of honey gel on cesarean incision pain: a triple blind clinical trial. *Afr J Pharm Pharmacol* 2013;7:19-24.
- [51] Heidari T, Roozbahani N, Farahani LA, Attarha M, Torkestani NA, et al. Does iranian astragalus gossypinus honey assist in healing caesarean wounds and scars? *Eur J Integr Med* 2013;5:226-233.
- [52] Ali A, Sarhan HA, Magdy T. Preparation and characterization of phenytoin sodium niosomes for enhanced closure of skin injuries. *Int J Pharm Pharm Sci* 2014;6:542-546.
- [53] Ahmed AKJ, Hoekstra MJ, Hage JJ, Karim RB. Honey-medicated dressing: transformation of an ancient remedy into modern therapy. *Ann Plast Surg* 2003;50:143-48.
- [54] Nikpour M, Shirvani MA, Azadbakht M, Zanjani R, Mousavi E. The effect of honey gel on abdominal wound healing in ce-

- sarean section: a triple blind randomized clinical trial. *Oman Med J* 2014;29:255-259.
- [55] Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, et al. Breast cancer: biology, biomarkers, and treatments. *Int Immunopharmacol* 2020;84:106535.
- [56] Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J* 2013;15:195-218.
- [57] Wang Y, Yu J, Cui R, Lin J, Ding X. Curcumin in treating breast cancer: a review. *J Lab Autom* 2016;21:723-731.
- [58] Aghamohammadi D, Fakhari S, Bilehjani E, Hassanzadeh S. The effects of honey and cinnamon mixture on improving the quality of life in breast cancer. *Crescent J Med Biol Sci* 2017;4:74-79.
- [59] Darvishi N, Yousefinejad V, Akbari ME, Abdi M, Moradi N, et al. Antioxidant and anti-inflammatory effects of oral propolis in patients with breast cancer treated with chemotherapy: a randomized controlled trial. *J Herb Med* 2020;23:100385.
- [60] Niazi A, Rahimi VB, Soheili-Far S, Askari N, Rahmani-an-Devin P, et al. A systematic review on prevention and treatment of nipple pain and fissure: are they curable? *J Pharmacopunct* 2018;21:139-150.
- [61] Lv X, Feng R, Zhai J. A combination of mupirocin and acidic fibroblast growth factor for nipple fissure and nipple pain in breastfeeding women: protocol for a randomised, double-blind, controlled trial. *BMJ open* 2019;9:e025526.
- [62] Ghomian N, Mousavifar N, Rostami Nezhad V, Ghanaei N. Frequency of pregnancy and its predicting factors in IUI cycles at Milad Infertility Center during 2011-2013. *Iran J Obstet Gynecol Infertil* 2017;20:13-20.
- [63] Starosta A, Gordon CE, Hornstein MD. Predictive factors for intrauterine insemination outcomes: a review. *Fertil Res Pract* 2020;6:1-11.
- [64] Kavousi M, Ghaebi NK, Najafi MN, Mokaberinejad R, Feyzabadi Z, et al. The effect of a natural vaginal product based on honey on the success of intrauterine insemination (IUI) in infertility treatment. *Avicenna J Phytomed* 2019;9:310-321.
- [65] Abdelhafiz AT, Muhamad JA. Midcycle pericoital intravaginal bee honey and royal jelly for male factor infertility. *Int J Gynaecol Obstet* 2008;101:146-149.
- [66] Bansal V, Medhi B, Pandhi P. Honey--a remedy rediscovered and its therapeutic utility. *Kathmandu Univ Med J* 2005;3:305-309.
- [67] Kenda M, Glavač NK, Nagy M, Sollner Dolenc M, Oeonom. Herbal products used in menopause and for gynecological disorders. *Molecules* 2021;26:7421-741.
- [68] Israili ZH. Antimicrobial properties of honey. *Am J Ther* 2014;21:304-323.
- [69] Nasir N-AM, Halim AS, Singh K-KB, Dorai AA, Haneef M-NM. Antibacterial properties of tualang honey and its effect in burn wound management: a comparative study. *BMC Complement Altern Med* 2010;10:1-7.
- [70] Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. *Asian Pac J Trop Biomed* 2011;1:154-160.
- [71] Koenig T, Roh JLC. Healing wounds with honey. *Undergrad Res J* 2016;15:1.
- [72] Bogdanov S. The honey book. Bee product science Available in: <http://www.bee-hexagon.net/> Accessed. 2011;23:12.
- [73] Agbaje E, Ogunsanya T, Aiwerioba O. Conventional use of honey as antibacterial agent. *Ann Afr Med* 2006;5:78-81.
- [74] Medhi B, Puri A, Upadhyay S, Kaman L. Topical application of honey in the treatment of wound healing: a metaanalysis. *JK Sci* 2008;10:166-9.
- [75] Subrahmanyam M. Topical application of honey in treatment of burns. *Br J Surg* 1991;78:497-498.
- [76] Anyanwu C. Investigation of in vitro antifungal activity of honey. *J Med Plant Res* 2012;6:3512-3516.
- [77] Al-Waili NS, Salom K, Butler G, Al Ghamdi AA. Honey and microbial infections: a review supporting the use of honey for microbial control. *J Med Food* 2011;14:1079-1096.
- [78] Canonico B, Candiracci M, Citterio B, Curci R, Squarzone S, et al. Honey flavonoids inhibit *Candida albicans* morphogenesis by affecting DNA behavior and mitochondrial function. *Future Microbiol* 2014;9:445-456.
- [79] Mohan A, Quek S-Y, Gutierrez-Maddox N, Gao Y, Shu Q. Effect of honey in improving the gut microbial balance. *Food Qual Saf* 2017;1:107-115.
- [80] Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns* 1998;24:157-161.
- [81] Hussein SZ, Mohd Yusoff K, Makpol S, Mohd Yusof YA. Gelam honey attenuates carrageenan-induced rat paw inflammation via NF- $\kappa$ B pathway. *PLoS One* 2013;8:e72365.
- [82] Hussein SZ, Mohd Yusoff K, Makpol S, Mohd Yusof YA. Gelam honey inhibits the production of proinflammatory mediators NO, PGE2, TNF- $\alpha$ , and IL-6 in carrageenan-induced acute paw edema in rats. *Evid-based Complement Altern Med* 2012;2012:109636.
- [83] Candiracci M, Piatti E, Dominguez-Barragan M, Garcia-Antras D, Morgado B, et al. Anti-inflammatory activity of a honey flavonoid extract on lipopolysaccharide-activated N13 microglial cells. *J Agric Food Chem* 2012;60:12304-11.
- [84] Ahmed S, Othman NH. Honey as a potential natural anticancer agent: a review of its mechanisms. *Evid-based Complement Altern Med* 2013;2013:829070.
- [85] Erejuwa OO, Sulaiman SA, Ab Wahab MS. Honey: a novel antioxidant. *Molecules* 2012;17:4400-4423.
- [86] Nagai T, Sakai M, Inoue R, Inoue H, Suzuki N. Antioxidative activities of some commercially honeys, royal jelly, and propolis. *Food Chem* 2001;75:237-240.
- [87] Al-Mamary M, Al-Meerri A, Al-Habori M. Antioxidant activities and total phenolics of different types of honey. *Nutr Res* 2002;22:1041-1047.
- [88] Miguel M, Antunes MD, Faleiro ML. Honey as a complementary medicine. *Integr Med Insights* 2017;12:1178633717702869.
- [89] Orsolici N, Knezević A, Sver L, Terzić S, Hackenberger B, Basić I. Influence of honey bee products on transplantable murine tumours. *Vet Comp Oncol* 2003;1:216-26.
- [90] Erejuwa OO, Sulaiman SA, Wahab MSA. Effects of honey and its mechanisms of action on the development and progression of cancer. *Molecules* 2014;19:2497-2522.
- [91] Fauzi AN, Norazmi MN, Yaacob NS. Tualang honey induces

- apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. *Food Chem Toxicol* 2011;49:871-878.
- [92] Ahmed S, Sulaiman SA, Othman NH. Oral administration of tualang and manuka honeys modulates breast cancer progression in sprague-dawley rats model eCAM. *Evid Based Complement Alternat Med* 2017;2017:5904361.
- [93] Jaganathan SK, Mandal M. Honey constituents and their apoptotic effect in colon cancer cells. *J Anal At Spectrom* 2009;1:29-36.
- [94] Akanmu MA, Olowookere TA, Atunwa SA, Ibrahim BO, Lami-di OF, et al. Neuropharmacological effects of Nigerian honey in mice. *Afr J Tradit Complement Altern Med* 2011;8:230-249.
- [95] Aziz C, Ismail C, Hussin C, Mohamed M. The antinociceptive effects of Tualang honey in male Sprague-Dawley rats: a preliminary study. *J Tradit Complement Med* 2014;4:298-300.