Review article

Anti-breast cancer potential of honey: a narrative review

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ABSTRACT

Cancer is responsible for the death of millions of people all around the world. Among the large group of cancers, the prevalence of breast cancer is highest in women. Therapeutic interventions, including removal surgery, radiation therapy, hormone therapy, and chemotherapy which is largely used, may cause adverse effects on the quality of patients' life. This fact has encouraged researchers to find natural substances such as honey to overcome harmful effects. Nowadays, honey is recommended for plenty of abnormalities because of its antioxidant, anti-inflammatory, and antimicrobial properties. Various studies have been conducted to explore the anticancer benefits of different types of honey from different origins. In this review, we are going to summarize in-vitro, animal, and human studies on the anti-breast cancer potential of honey.

Key words: honey, breast cancer, anticancer, complementary medicine

INTRODUCTION

Cancer is a disease characterized by uncontrolled cell growth due to many factors that cause mutation. Cancer cells can also damage other neighbor cells and tissues, leading to many adverse outcomes. According to the American cancer society, 1,762,450 cancer cases were diagnosed and 606,880 cancer-related deaths occurred in the US in 2020 [1]. Among the large group of cancers, breast cancer is the most common among women [2], which leads to 14% of cancer-related deaths. The probability of developing invasive breast cancer is 1 in 8 women [3]. Current therapeutic ways against breast cancer include removal surgery, radiation therapy, hormone therapy, and commonly used chemotherapy [4]. Each of these interventions has specialized advantages and disadvantages. Radiation can damage unfavorable cells in the affected area by influencing genetic contents [5]. However, due to its disability to separate healthy cells from cancer cells, patients may suffer from annoying symptoms during therapy or months and years later [6]. Chemotherapy which has the leading role in therapeutic modalities against cancer also causes a wide range of negative effects on the life quality of patients. These unwilling outcomes of invasive treatments have encouraged researchers to find natural substances such as honey to overcome harmful effects. Honey is a product of an intricate enzymatic process of nectar and saccharine secretions obtained from a wide range of floral sources [7]. The compounds may differ depending on honey's geographical origin, but the main composition is sugar, phenolic acid, amino acids, flavonoids, enzymes, and proteins [8]. Some medicinal benefits of honey are anti-inflammatory [9], antimicrobial [10], and antioxidant [11], effects. Anticancer properties of honey are related to its bioactive compounds such as phenolic acid, flavonoids, and polyphenols [12]. Although the exact procedure is unclear yet, some studies have shown bioactive compound's interference with antioxidant [13], anti-proliferative [14], and proapoptotic cell-signaling pathways [15]. In this article, we are going to review some studies conducted to investigate the therapeutic potential of honey for breast cancer classified into animal, human, and in vitro studies.

MATERIAL AND METHODS

This study was designed as a narrative review of in vitro, animal, and clinical trial articles that were published in English. The last search occurred on November 19th, 2020, and we searched them only in Google Scholar database with search strategy: all in the title: *Breast Honey Cancer OR Neoplasms OR Carcinoma*. We didn't use any other filters.

RESULTS

In vitro studies

Manuka honey

Multiple studies have been conducted to examine the cytotoxic effects of Manuka honey (MH) on breast cancer cells. According to Aryappalli et al. investigating the modulatory effects of MH on invasiveness, proliferation, and its angiogenic potential in breast cancer cells (MDA-MB-231 and MCF-7 cell lines) showed that breast cancer cell lines with exposure to MH at different concentrations had significant loss of viability which was controlled by the concentration of MH and time of exposure. Also, the viability of control groups decreased in high concentrations (2.5% and 5%) but to a lesser extent compared to the MH groups, while in low concentrations (1.25% and 0.6%) had no significant effect on proliferation at any time point. In MCF-10A cells (healthy cell lines) high concentrations were toxic but low concentrations showed no reduction in viability. Moreover, the capacity of MH to inhibit metastasis and colonization of MDA-MB-231 cells was demonstrated, and contact with MH induced mitochondria-mediated apoptosis [16]. Another study on MH and breast cancer conducted by Portokalakis et al. revealed a correlation between total phenolic content (TPC) and cytotoxicity induced by MH in MCF7 breast cancer cells. This study suggested that the TPC and *Unique Manuka Factor* (UMF) rating are strongly related and MH cytotoxicity against MCF-7 cells improved through rising UMF 5+ to UMF 15+ rating. Therefore, cytotoxic effects on MCF-7 cells are strongly correlated with TPC of MH samples. They also showed that MHs rated UMF 5+, 10+, 15+, and 18+ have higher TPC than most of the honeys cited in this article [17].

Considering the results from previous studies on MH, Wong et al. tested the effect of MH supplementation with hydrogen peroxide or/and iron (II/III) salts on the TPC of MH and the cytotoxicity against breast cancer cells. Moderate iron supplementation increased the cytotoxicity of MH toward MCF-7 cell line. And these cytotoxic effects were more sustained than cytotoxicity caused by hydrogen peroxide addition. Supplementation of MH with iron (III) or iron (II) salts at low dose resulted in decreased TPC while with the increase of the given dose, TPC also increased [18]. Moreover, a cytokine named interleukin-6 (IL-6) has pleiotropic functions in regulating the differentiation and growth of breast cancer cells [19]. IL-6 indirectly catalyzes tyrosine phosphorylation of signal transducer and activator of transcription 3 (STAT3). STAT3 is a transcription factor that initiates a complex transcriptional set promoting cell growth and inhibiting apoptosis [20]. Regarding these data and a previous study [16], Aryappalli et al. investigated the mechanism of MH affecting breast and lung cancer cells. They indicated that exposure to MH causes a decrease in p-STAT3 levels

by competing with IL-6 for binding to its receptor, they also revealed that the compounds mainly responsible for this effect are flavonoids in MH (luteolin, quercetin, chrysin, and galangin), that each shows a high capacity to inhibit p-STAT3 [21]. The result of this study was similar to Al Qubaisi et al. reported findings. Based on their study, the treatment of cancer cells (MDA-MB-231) with honey inhibited the STAT3 pathway in a time and dose-dependent manner, decreased the IL-6 production and anti-apoptotic level of Bcl-2 protein, and also increased cytochrome C protein expression which eventually led to cancer cells' death. The function of heated MH as a temperature treatment was also observed but did not affect STAT3 phosphorylation and cytocidal capacity [22].

Tualang honey

Several studies have been conducted to explore the capacity of Tualang honey (TH) in inhibiting processes advancing to cell death. Yaacob et al. reported that TH contains various compounds such as phenolic acids, flavonoids and has significant anti-cancer activity against breast cancer cell lines, comparable to the effect of tamoxifen in vitro. Honey increased the anti-cancer activity of tamoxifen in responsive and nonresponsive estrogen receptors in breast cancer cell lines. Also, cytometric flow analysis and fluorescence microscopy showed an acceleration in the process of apoptosis of breast cancer cell lines and the activation of caspase 3/7, 8 and 9. Mitochondrial membrane depolarization was also increased in breast cancer cell lines due to using of honey combined with tamoxifen. Therefore, TH with tamoxifen can be used as an alternative to treat breast cancer, reduce the required dose of tamoxifen, and consequently, reduce tamoxifen's side effects [2].

Fauzi et al. conducted a study to evaluate the effect of TH on breast cancer cells (MCF-7 and MDA-MB-231) treatment with 1% TH caused cell cycle halt at G2/M and S phases in MCF-7 and MDA-MB-231 cells, respectively. Significant changes in the expression of apoptosis-related genes were observed in MCF-7 cells including the increase of p53, p21 and Fas-associated death domain (FADD) proteins. However, these changes were not significant in MDA-MB-231 cells, an increase in tumor necrosis factor receptor type 1 associated death domain (TRADD), FADD, and p21 proteins was still observed [23]. Following these results Fauzi et al. studied the effect of TH on MCF-7 and MDA-MB-231 cancer cells under the influence of a specific dose of honey (1–10%). Their findings showed the cytotoxic activity of TH against breast and cervical cancer cell lines with an efficient concentration (EC50) of 2.4–2.8%. The leakage of lactate dehydrogenase from honey-treated cell membranes was increased. Honey increased apoptosis in cervical and breast cancer cells and decreased mitochondrial membrane potential in cancer cells after 24 h of treatment. Caspase 3/7 and 9 activation was also observed in all cells treated with honey indicating the role of the mitochondrial apoptotic signaling pathway in advancing cell death. Thus, they reported that this kind of honey has anti-cancer properties against cervical and breast cancers due to compounds such as antioxidants, vitamins, and phenols [24]. Overall, these in vitro studies indicated TH's ability to modulate signaling pathways and its potential as a valuable ingredient in preventing breast cancer.

Others

Badria et al. studied the effect of different honeybee related natural products including 15 types of honey found in Egypt on different cancer cells, in MCF-7 (breast cancer cells). Results showed the highest inhibition activity (52.53%) and best efficacy for citrus honey, followed by cotton (45.93%), sesame and sunflower (8.47%), and acacia honey with the lowest inhibition activity (2.53%) [25]. In 2018, Almeer et al. studied the effect of two types of honey (wild and sidr honey) on the proliferation, cell morphology, and expression of two genes in MDAMB-231 cell line (breast cancer cells). this study had 4 groups: untreated cells (negative control: group 1), cells treated with doxorubicin at 4% concentration (Doxo) (positive control: group 2), cells treated with sidr honey at 1% concentration (H1: group 3), and cells treated with wild honey at 1% concentration (H2: group 4). Each group divided into three subgroups (6, 24 or 48 h). Results confirmed that cell morphology changed after treatment with H1 and H2. The changes were observed 48 h after treatment, results of the methyl thiazolyl tetrazolium (MTT) assay highlighted the cytotoxic effect of both kinds of honey on breast cancer cell line. While less effective than Doxo in eliminating the cancer cells, both Wild and sidr honey have the potential to promote apoptosis in triple-negative breast cancer cells after 48 h of treatment [26].

Moreover, two similar studies by Seyhan et al. with slight differences investigated the effect of pine, cedar, chestnut, and multifloral honey on MCF10A cell line as control and three different cell lines from different types of breast cancer. Cytotoxicity induced by chestnut honey was over 50% on all cell lines, even with low dosage. Cedar honey was the second effective honey and it was highly effective on MCF7, and MCF10A but had no significant effect on MDAMB 231 cell line. Pine honey appeared very effective on MDAMB 231 cell line in 1 mg/mL dose. It also showed anti-cancer effects on SKBR3 and MCF-7 cell lines in 2.5–5 mg/mL dose range. These tree-originated honeys improved the viability of control cells in 2.5–5 mg/mL dose range, while their cytotoxic effect on MCF10A cell line was reported only in higher doses (10 mg/mL). Besides, artificial and multifloral honeys were mostly

not able to decrease viability except in SKBR3 cell line and even led to an increase of the cell viability in 1–5 mg/mL doses. Analyzing these honeys showed that the TPC of them decreases in the order of chestnut and cedar, pine, and multifloral, which is compatible with their dark color and cytotoxic affectivity. According to obtained results, chestnut and cedar honeys had the most cytotoxic effect on all cell lines, while pine honey had appropriate toxicity on the cancer cells and was the least toxic honey against control cells [27].

In one of the latest articles about honey and breast cancer conducted by Celebioglu et al. the effect of chestnut honey and its combination with probiotics on breast and colon cancer cell lines was investigated. Different dilutions of honey were tested on MCF7, MCF-10A, and Caco-2 cells. Results showed that the honey itself did not change the viability in MCF-7 cells at dilutions of $1/_{10}$ and ⅕; however, supernatants of *Lactobacillus acidophilus* LA-5 from the control group (grown on glucose) or honey group (grown on honey) significantly reduced the viability of cells by 20–30%. When using a dilution of ½ *L. acidophilus* and added chestnut honey reduced the viability of cells. Examination of MCF-10A cell lines (non-neoplastic cell lines) showed that only dilution of ½ reduced the viability (about 20%). Based on the results of testing the *Lactobacillus rhamnosus* GG supernatants only the bacteria grown with chestnut honey decreased the viability of cancer cells and reduction with a dilution of ½ was more than 80%. Besides, in healthy cells using chestnut honey as a carbon source, honey reduced the effect of *L. rhamnosus* GG with ½ and ⅕ dilutions. Thus, compared to chestnut honey alone or probiotics grown on glucose, the viability of breast cancer cells was more reduced using probiotics grown on chestnut honey [28].

Moreover, Tsiapara et al. studied the effect of honeys acquired from thyme, pine, and fir plants on MCF-7 (breast cancer), Ishikawa (endometrial), and PC-3 (prostate) cell lines. The results indicated that all the studied honeys contained hydroxymethylfurfural, total phenolics, phenolic acids, sugars, and volatile compounds. Thyme honey contained a higher amount of these ingredients compared to other honey. Thyme, pine, and fir honey displayed anti-estrogenic and limited estrogenic effects at low and high concentrations on MCF-7 cell lines, respectively. Thyme honey reduced the viability of PC-3 and Ishikawa cells, while fir honey stimulated the survival of MCF-7 cells [29].

Furthermore, in a study by Alhamdi et al. cytotoxic activity of plant extracts (Lemon Balm, Wormwood, Costus, and Guava) and honey was explored on the cell lines of breast, lung, and colon cancers. They reported that the extract of medicinal plant Guava compared to other plant extracts had intense cytotoxic activity against all three cell lines of breast, lung, and colon cancers, while Costus extract exhibited the weakest cytotoxic activity against all three cell lines. Also, honey displayed some effects on SW620 and A549 cell lines, only when used at the highest concentration (50 µg/µL) [30]. Nevertheless, further research should be done on guava extract and honey to investigate their active ingredients and action mechanism as anti-tumors (table 1 summarizes the anti-breast cancer effects of honey in in vitro studies).

IN VIVO STUDIES

Along with in vitro studies, several studies were performed on animal samples to achieve more practical results. In 2 studies by Ahmed et al. the effects of honey on breast cancer in rats have been examined. They had been injected with 1-methyl-1-nitrosourea (MNU), which is a highly reliable carcinogen and some of them were treated by TH. It has been observed that size, number, weight, and progression speed in tumors decreased in TH-treated rats. Besides, a reverse connection between pro- and anti-apoptotic expressions as well as changes in hematological parameters and estrogenic activity was reported after treatment with TH. Accordingly, it was concluded that TH could reduce breast carcinogenesis [31]. Furthermore, it has been assumed that MH and honey sugars analogue (HSA) along with TH, also have "cancer-preventive" properties. For examining their preventive effects on cancer, Ahmed et al. performed a study in which honey was given one week prior to MNU-induction resulted in a lower tumor incidence compared to those groups of rats which had not been given honey. This observation supports the preventive effects of MH and HSA on cancer [32]. Moreover, Banik et al. assessed the effects of crude honey, TH and MH, on cancerous rats induced by MNU. They examined the histopathology of female rats that were distributed into 4 groups: group 0 (normal), group 1 (MNU control), and group 2 and 3 (TH and MH treated). There were significant histological differences between sections of non-treated and treated rats favoring the tumor degradation in TH and MH treated group. By interpreting observed data, it has been found that crude honey can be used as an anticancer agent for breast cancer [33]. Takruri et al. and Kadir et al. conducted similar research on multi-floral honey except that they used a different carcinogen agent called 7,12 dimethylbenz(α)-anthracene (DMBA). Rats in the positive control group and honey group unlike the negative control group were given a diet containing DMBA and the honey group received honey in addition to the shared diet. After several weeks all rats were euthanized and histopathology examination of both groups was done. The results revealed that there was a reduction in the occurrence rate,

Table 1. In vitro/in vivo studies on the anti-breast cancer potential of honey.

In vitro/in vivo studies	Result	References
Assessing the molecular targets influenced by MH in some breast cancer cell lines (MDA-MB-231, MCF-7).	Induction of apoptosis in MDA-MB-231 cells mediated by MH through triggering caspases 8, 9, 6 and 3/7. This outcome is related to loss of Bcl-2 and enhanced Bax protein expression. MH also triggers apoptosis of MCF-7 cells by activating caspases 9 and 6. MH at low concentrations (0.03–1.25% w/v) induced sudden depletion of tyrosine-phosphorylated STAT3 (pY-STAT3) and reduced the IL-6 synthesis in MDA-MB-231 as well as MCF-7 cells. Migration and invasion were inhibited by MH in MDA-MB-231 cells. In conclusion, the IL-6/STAT3 signaling pathway is affected by MH in human breast cancer cells.	Aryappalli et al. [16]
Assessing the cytotoxicity of MH on breast cancer cell line (MCF-7) in correlation with MH total polyphenols content and antioxidant power.	The TPC varied from 1367 ± 152–2358 ± 79 mg GAE/kg. The antioxidant power varied from 170 ± 22–266 ± 21 mg GAE/kg. Dose-dependent cytotoxic activities in MCF-7 cells after MH treatment are reported. Cytotoxic effects of MH were remarkably in accordance with the TPC values (R2 = 0.99) as well as its antioxidant power (R2 = 0.95).	Portokalakis et al. [17]
MCF-7 cell line was exposed to MH graded UMF 18+ in addition to hydrogen peroxide and iron (II, III)	The addition of MH to iron showed both increase and decrease of TPC (time dependent), but hydrogen peroxide itself had no apparent effect on TPC. Hydrogen peroxide and iron (II, III) improved the cytotoxic effects of MH at low doses. Iron II had more cytotoxic effects than iron III.	Wong et al. [18]
Assessing the effect of MH on tyrosine-phosphorylated STAT3 inhibition and IL-6 receptor in human breast cancer cell line (MDA-MB-231) as well as lung cancer cell line (A549).	MH binds to IL-6R (~60%) so inhibits IL-6 to bind but it does not bind to IL-11R and IL-8 R. It did not change the tyrosine-phosphorylated or sCr family kinases. four of five major MH flavonoids (luteolin, quercetin, galangin, and chrysin) clearly bind to IL-6 R (at the highest concentration (50 M) used, 30–35% blocking IL-6 binding), but one of them (pinocembrin) did not. p-STAT3 was inhibited in a dose-dependent manner by each flavonoid. IL-6R blockade is a mechanism for the anti-tumor activity of MH and its flavonoids and is most likely inhibit p-STAT3.	Aryappalli et al. [21]
Assessing the apoptosis and mitochondrial membrane disruption by TH in human breast cancer cell lines (MCF-7, MDA-MB-231) as well as cervical cancer cell line (Hela cells)	TH with effective concentrations (2.4–2.8%) triggered cytotoxic activities and apoptosis in mentioned cancer cell lines. The mitochondrial membrane potential was reduced by TH 24h after the treatment of cancer cell lines. Caspase 3/7 and -9 were activated in all treated cancer cells indicating the involvement of mitochondrial apoptotic pathway.	Fauzi et al. [23]
Assessing the effects of TH combined with tamoxifen in promoting cell death in MCF-7 and MDA-MB-231 breast cancer cell lines.	The anticancer activity of TAM was promoted by TH in both MCF-7 and MDA -MB-231 cell lines. Combined treatment with TH and TAM activated caspase 3/7, 8, and 9 in correlation with rapid apoptosis especially in MDA-MB-231. Using TH in combination with TAM enhanced the depolarization of mitochondrial membrane in mentioned cell lines compared to treatment with TAM alone.	Yaacob et al. [2]
MCF-7 (estrogen receptor-dependent) and MDA-MB-231 (estrogen receptor-independent) breast cancer cell lines were exposed to TH.	TH properly blocked the growth cycle of cells at G2/M phases in MCF-7 cells and S phase in MDA-MB-231 cells. TH enhanced the expression of p21, p53, and other pro-apoptotic genes and reduced ERβ expression in MCF-7 cells in contrast to MDA -MB-231 which reduction of ERβ expression and increase of p21, p53, and other pro-apoptotic genes expression were not reported after 24 h treatment. TH reduced in MCF-7 cells but not in MDA-MB-231 cells after being in contact with TH for 48 h. Furthermore, FADD and TRADD (molecules that induce apoptosis through a receptor) expression increased in treated MDA-MB-231 while, unlike FADD, TRADD expression decreased in MCF-7 cells.	Fauzi et al. [24]
Assessing cytotoxic effects of honey bee products (honey, venom, and propolis) on MCF-7 breast cancer cell lines.	Italian BV in comparison to other bee venom acts more effectively as a cytotoxic agent in MCF-7 breast cancer cell lines especially the dissected one (with 90.17% inhibition) and cytotoxic effects of propolis types decrease in the order of Libyan propolis (with 83.57% inhibition) and Bulgarian powder propolis (with 75.65% inhibition). Citrus honey (with 52.53%% inhibition) and cotton honey (with 45.93% inhibition) have remedial effects on MCF-7 breast cancer cell lines.	Badria et al. [25]

Assessing some gens expression and cell survival and proliferation of MDA -MB-231 breast cancer cell lines that were exposed to sidr and wild honey.	Diminishing cell survival and proliferation by 48% and 91%, respectively, for sidr and wild along with the reduction of TIMP-1, TIMP-2, TIMP-4, MMP-9, and MMP-2 expression after being exposed to them for 48 h.	Almeer et al. [26]
Assessing the anti-carcinogenic effects of five Turkey honey types on MCF-7, MDA -MB-231, and SKBR3 cancer cell lines.	Cell proliferation assay represented high significant results in all cancer cell lines treated with chestnut honey at every dose. Cedar and pine honey showed statistically remarkable effects on cell viability/toxicity in all cell lines except when used in lower doses (1%). In such doses, no significant results were reported in MDA-MB-231 cells. Flower and artificial honey showed significant cytotoxic activity only against SKBR3 cells.	Seyhan et al. [27]
Assessing cytotoxic effects of pine, chestnut cedar, and multifloral honey on MCF7, MDAMB-231, SKBR3, and fibrocystic breast cancer cell lines in comparison to MCF10A control cells.	Phenolic component, antioxidant and cytotoxic effects of the honey types decrease in order of Chestnut, Cedar, Pine, and multifloral honey Chestnut honey induces 50% cytotoxicity on each cell line. Like chestnut, cedar showed 50% cytotoxic activity but at higher doses. Pine honey caused cytotoxicity only at low doses. Multifloral honey had moderate cytotoxic effects on SKBR-3 and MDA-MD-231 if given at high doses.	Seyhan et al. [28]
Assessing the cytotoxicity effect of probiotic bacteria grown with chestnut honey, on breast cancer and colon cancer cell lines (MCF-7, Caco-2).	Chestnut honey affected the probiotic bacteria positively by increasing the growth and modulating the properties of probiotics such as autoaggregation as well as surface hydrophobicity. The cytotoxicity effects of such probiotics are much more compared to probiotics or honey alone.	Celebioglu et al. [29]
MCF-7 cell line was exposed to thyme, pine, and fir honey	These types of honey have a synergistic effect at high dosage and antagonist effect at low dosage on oestrogen. Thyme and pine honey do not affect cell viability while fir honey increased it.	Tsiapara et al. [30]
50 nulliparous female Sprague-Dawley 28–35-day-old rats were given 80 mg/kg MNU and 0.2–2.0 g/kg body weight of TH in different groups.	Significant decrease in tumor development and numbers, occurrence, volume, and weight of the tumor mass.	Ahmed et al. [32]
30 Sprague-Dawley female rats aged between 28 and 33 days were induced by the carcinogen MNU 80 mg/kg and some of them were given 1.0 g/kg body weight/day of TH and MH.	Decrease in tumor volume, weight, numbers, and growth rate.	Ahmed et al. [33]
130 female Sprague-Dawley rats in 6 groups were given MNU and randomly 0.2–2.0 g/kg body weight of TH, 1.0 g/kg of MH, and 1.0 g/kg HAS.	Fewer cases with cancer progression in the treated group and decrease in volume, weight, occurrence, and tumor numbers.	Ahmed et al. [34]
40 female Sprague-Dawley 28–33-day -old rats in 4 groups were given 80 mg/kg MNU and randomly 1 g/kg body weight/day of TH and MH.	Decreasing in tumor volume, weight and numbers, and growth rate.	Banik et al. [35]
39 female Sprague-Dawley rats), three weeks of age (40–45 g) in two groups (positive and honey group) were fed DMBA with a dose of 80 mg/kg body weight, and the honey group was fed 50 g/kg of multifloral honey.	Significant decrease in the mammary cancer occurrence, number of palpable tumors, tumor volume, and weight.	Takruri et al. [36]
40 female Sprague-Dawley 45–48-day -old rats in 4 groups were given 80 mg/kg DMBA and 0.2–2.0 g/kg body weight/day of TH for 150 days.	Slower increase of tumor volume, smaller mean tumor volume, and fewer cases with cancer progression in the treated group.	Kadir et al. [37]

TIMP – tissue inhibitor of metalloproteinase; MMP – matrix metalloproteinase; G2 phase – Gap2 phase; M phase – mitosis phase; S phase – synthesis phase; BV – bee venom; UMF – Unique Manuka Factor; MH – Manuka honey; TPC – total phenols content; TH – Tualang honey; P53 – preventing genome mutation; Erβ – estrogen receptor β; sCr – serum creatinine; FADD – Fas-associated death domain; TRADD – tumor necrosis factor receptor type 1 associated death domain; IL-6 – interleukin-6; IL-6Rα – IL-6 receptor α chain; IL-8R – IL-8 receptor; IL-11Rα – IL-11 receptor α chain; STAT3 – signal transducer and activator of transcription 3; p-STAT3 – tyrosine-phosphorylated STAT3; pY-STAT3 – phosphorylated STAT3; TAM – tamoxifen; DMBA – 7,12-dimethylbenz(α)anthracene; MNU – 1methyl-1-nitrosourea; HAS – honey sugars analogue.

number, size, and weight of tumors in the honey group. So, it has been proved that honey has protective effects against DMBA-induced breast cancer [34] (table 1 summarizes the anti-breast cancer effects of honey in in vivo studies).

CLINICAL TRIALS

The first clinical trial providing evidence about the effectiveness of TH for breast cancer was conducted by Hizan et al. in Malaysia to show TH adjunct with anastrozole improve background parenchyma enhancement (BPE). In this study, 22 postmenopausal women with ER-positive breast cancer were divided randomly into two groups: group 1 with 1 mg/24 h anastrozole and group 2 with 1 mg anastrozole + 20 mg TH per day. The average patient age was 59 ± 5.9 years, and the average menopausal age was 50 ± 3.0 years; all patients had normal menopause. By considering the MRI photos, it became clear that in the control group and treatment group, respectively, 10% and 41.7% of the patients showed a decrease in BPE. But these reductions are qualitative and do not provide quantitative information [35]. To explore the association between honey and safety conditions of menopausal women with breast cancer, a randomized control trial study was conducted by Zakaria et al. in Malaysia. The honey used in this study was TH, which has high antioxidant power due to its significant amount of flavonoids, phenolics, and free radical scavenging activity. Before the intervention, fasting blood samples were taken from individuals for hematological and chemical evaluation. They divided the participants into two groups of control and honey, and the honey group was fed 20 g/24 h of honey for 12 weeks. Based on the results, it was observed that the amount of white blood cells and blood platelets in the honey group has increased. Besides, the amount of alanine aminotransferase was higher in the control group compared to the honey group, and since the increase in liver enzymes indicates liver failure, it can be understood that honey has a protective effect on the liver in breast cancer patients. Also, in this study, unlike the previous study on healthy postmenopausal people for 4 months, [36] the creatinine levels increased in both control and honey groups, which may be due to differences in the duration of the study or its participants [37]. Moreover, the effect of Dorsata honey on IL-3 levels in patients undergoing chemotherapy was investigated by Kurniawan et al. They divided 30 breast cancer patients with prescribed chemotherapy, aged between 23–61 years and the average age of 47.3 (±7.5) years, into two groups of 15 patients. This high average age is due to the higher incidence of breast cancer in people over 40 years old [42]. The honey group was fed 15 mg of Dorsata, 3 times a day for 15 days. Blood samples were taken for evaluation twice, pre-intervention (before the start of chemotherapy) and post-intervention (after the end of chemotherapy). The first sampling showed that the level of IL-3 in the honey group and control group was 70.07 pg/dl and 88.88 pg/dl, respectively, while the level of IL-3 during the second sampling was 143.46 pg/dl in the honey group and 84.36 pg/dl in the control group. Further examination of obtained results showed that the amount of IL-3 in the honey group increased by 104.7% and decreased in the control group by 5.1% [39].

In line with these studies, Munstedt et al. explored the effect of honey and a mixture of honey and bee pollen on reducing menopausal symptoms in breast cancer patients. Anti-hormonal therapies with tamoxifen, aromatase inhibitors/inactivators increased some menopausal symptoms including pain. And because breast cancer patients cannot use estrogen and similar substances to prevent the disease from progressing or recurring. Options to reduce patient complaints are limited. In this perspective, randomized crossover trial patients were divided into two groups: honey group (who received pure honey used as a placebo because no research had been done on the effect of honey at the time of the study) and pollen group (who received a mixture of pollen and honey). Each group consumed one tablespoon of their given substance for 14 days and after the end of the period, blood samples and MRS were taken from them. Then, after 14 days with no intervention, patients received the substance of the opposite group for 14 days and the evaluations were performed again. The rate of symptom improvement was 68.3% in the honey and 70.9% in the pollen group, indicating no significant difference between them. Based on the MRS taken from participants before and after the intervention, it was found that honey consumption is highly effective for patients receiving aromatase inhibitors/inactivators but increases their oestradiol levels. Also, pollen consumption showed greater clinical progress in patients taking tamoxifen. Overall, this study showed that honey pollen and honey are both effective in reducing menopausal symptoms in breast cancer patients, but the increase of serum oestradiol in the honey group should be considered [40].

Furthermore, in another clinical trial that was conducted in Iran, Aghamohammadi et al. selected 117 female patients with pre-diagnosis of breast cancer aged between 34–60 years (average 48.58 [±7.6] years) to evaluate the health status and patients' quality of life, one week before and after receiving a mixture of honey and cinnamon. To this end, participants were given EORTC QLQ-C30, a 30-item questionnaire selected by the European Organization for Research and Treatment of Cancer, to evaluate patients' life quality pre-and post-intervention (selected items can be found in the main article). Participants consumed a mixture of honey (30 g) and cinnamon powder (4 g) dissolved in a cup of

boiling water, three times a day for a week. Then they were asked to fill the questionnaire again and results were assessed. 23 of the 30 items were improved, but no improvement was found in other items such as dyspnea, diarrhea, interference of disease with family life, performance and status in strenuous activities, difficulty in daily concentration, vomiting, and difficulty in remembering things [41] (table 2 summarizes the anti-breast cancer effects of honey in human trials).

Table 2. Clinical trials of the anti-breast cancer potential of honey.

Human trials/dosage	Results	Reference
30 subjects were randomly divided into two groups: the intervention who received anastrozole (1 mg) along with TH (20 g) per day and the control group took only anastrozole (1 mg) per day. The BPE was assessed ahead and 6 months after the treatment.	Receive of anastrozole alone in the control group resulted in the change of BPE type from intermediate to low by a 10% decrease. Receive of the anastrozole and TH mixture in the participants resulted in a decrease of 42% in BPE.	Hizan et al. [38]
72 postmenopausal female participants with stage I, II, or III breast cancer were randomly divided into two groups: a control group (no honey) and a honey group (20 g/24 h of honey for 12 weeks). The dose is equivalent to one tablespoon of honey.	Significant higher amount of alanine aminotransferase in the control group than in the honey group was reported after treatment. Increase in creatinine levels, white blood cell, and platelet counts in the honey group after treatment.	Zakaria et al. [40]
The populations consisted of 30 breast cancer patients (2361 years old), divided into two groups. 15 subjects, as an intervention group, received Dorsata honey at a dose of 15 ml (two tablespoons) orally, 3 times a day for 15 days. The control group was prescribed nourishing foods and vitamin supplements.	Observation by ELISA showed a significant increase in mean IL3 levels, which is a multi-potential hematopoietic growth factor. Honey supplementation increased IL3 levels in breast cancer patients who underwent chemotherapy.	Kurniawan et al. [42]
A total of 46 subjects (age > 18 years) with severe menopausal complaints, assessed by the MRS, were enrolled. The instruction was to take in a tablespoonful of either substance (honey or pollen) for the following 14 days. After an assessment and at least 14 days of break, the patients received the other substitute for a further 14 days.	70.9% (22/31) of the patients reported a significant improvement while taking pollen and 68.3% (28/41) also stated progress after treatment with honey. Unexpectedly, a non-significant difference between the cytotoxic effect of honey and pollen was seen and they both had similar effects. Compared to patients who were treated with tamoxifen, honey exhibited a considerable improvement in symptoms.	Munstedt et al. [43]
A group of 119 female patients with breast cancer (20–60 years old) were given a mixture of honey (a tablespoon, 30 g) and cinnamon (a teaspoon, 4 g) powder. The mixture was dissolved in a cup of heated water and the participants took it three times a day for one week.	Patients' quality of life was assessed before and after the intervention through the EORTC QLQ-C30 questionnaire. The results showed a significant progression in most (23/30) of the criteria referring to the quality of life.	Aghamohammadi et al. [44]
A population of 135 BC patients were assigned to three main groups. Two groups received chemotherapy followed by radiation therapy. 45 subjects were supplemented with propolis capsules (400 mg, 3 times daily) for 10 continuous days before radiotherapy, during radiation treatment, and 10 days after radiotherapy.	Significant decrease in the DNA damage induced by radiation. Inhibition of RRM2 subunit overexpression. Serum MDA and TAC considerably improved. WBCs, platelet counts and HB concentration became within the normal control level.	Mohamed et al. [48]
86 patients (81 were included in the results) were randomly given either MH or standard aqueous cream. The instruction was to apply two times a day, from the first day of radiation until day 10 after treatment.	Non-significant (21%) fewer dermatitis occurrence of grade > 2 in the honey group. A tendency towards a lower incidence rate of grade > 2 dermatitides over a week, in the honey-treated group. Patients who had received honey reported more ease of use and comfort.	Tan et al. [49]
24 skin reactions (in 21 patients with grade 3 skin toxicities) were evaluated. Half of which were given honey gauze once a day and the control group received paraffin.	Honey gauzes can be used to treat dermatitis induced by radiotherapy. The daily VAS revealed faster healing of skin reactions and irritation, less itching, and less pain, in the honey group compared to the paraffin population. No related side effects were reported.	Moolenaar et al. [50]

BC – breast cancer; RRM2 – ribonucleotide reductase M2; MDA – malondialdehyde; TAC – total antioxidant capacity; WBCs – white blood cells; HB – hemoglobin; MRS – Menopause Rating Scale; IL3 – interleukin 3; VAS – visual analogue scale; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer questionnaire; BPE – background parenchymal enhancement.

CONCLUSION AND FUTURE PERSPECTIVE

Breast cancer is the second leading cause of cancer death in women (only lung cancer kills more women each year). The chance of dying from breast cancer is about 2.6%. In the last 40 years, many plants, seafood, and microorganisms have been used to treat diseases and increase life satisfaction [42]. Honey has biological properties such as antioxidant [43], anti-proliferative, anti-bacteria [44], and anti-cancer [23]. In vitro experiments examined the antioxidant ability of honey and found that honey reduced the proliferation of breast cancer cells and also increased apoptosis in them. Moreover, animal studies have shown that honey, duo to its cancer-preventing properties, reduces the number, speed of growth, volume and weight of tumors. Also, the results of clinical trials indicated that honey is effective in increasing the IL-3 levels, number of blood cells, and quality of life as well as reducing menopausal symptoms. Nevertheless, these studies showed honey caused no alteration in blood creatinine levels. Whereas it increased serum estradiol levels, which should be considered if honey is going to be used. Although in most studies reported in this paper, honey consumption was associated with the modification of breast cancer, still more studies, especially animal studies and clinical trials, are needed to confirm the effect of honey on the treatment and prevention of breast cancer.

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PRACTICE POINTS

- Anti-breast cancer potential of different types of honey has been tested in several studies.
- Honey can exert its anti-cancer potential through its anti-inflammatory and antioxidant effects.
- Manuka honey can lead to breast cancer cell apoptosis through decreasing production of intrerlukin-6 and inhibiting signal transducer and activator of transcription 3 (STAT3) pathway.
- Tualang honey increases the anti-cancer activity of tamoxifen.
- Tamoxifen together with Tualang honey activates multiple caspase enzymes and increases mitochondrial membrane depolarization which leads to breast cancer cell apoptosis.
- The anti-breast cancer effects of honey have been proved in in vitro, in vivo and human studies.

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