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Honey-based therapeutics: a comprehensive review of anticancer, antioxidant, and prognostic impacts in breast cancer treatment

Abstract

Background: Nowadays, breast cancer is one of the main causes of deaths among women worldwide. It represents a major challenge in healthcare systems. With the increasing rates of mortality and the adverse effects of conventional therapy, a prompt insight into honey-based therapeutics was crucial for developing new effective complementary and alternative medicine. As a natural product with its long history use in traditional medicine, honey has drawn the attention of thousands of scientists over the past few years for treating various types of cancers, particularly breast cancer. Its anticancer properties are mainly attributed to its complex composition and valuable phyto compounds.

Methods: In this review, our study sheds light on honey-based therapeutics for their anticancer properties, antioxidant potency, and its prognosis impact in breast cancer patients referring to bibliographical data collected from 2020 to 2024.

Discussion: Several studies unveiled the outstanding potential of honey to modulate apoptosis, immune response, and inflammation processes. Its healing powers could also be explained by its antioxidant potency and preventive effects against oxidative stress which often causes cancers. Similarly, its remarkable prognosis effects on breast cancer patients have been widely debated. Honey does not only improve the life quality of patients undergoing chemotherapy by reducing its side effects but also increases their survival rates.

Conclusion: Honey represents a promising complementary therapy that could enhance the effectiveness of conventional breast cancer treatments.

Keywords: honey, honey-based therapeutics, anti-cancer properties, antioxidant properties, prognostic impact

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Introduction

Nowadays, cancer represents one of the leading causes of deaths worldwide. The epidemiological and demographic transitions, the process of population ageing, lifestyle changes and environmental factors have greatly contributed to the prevalence of cancer. Each year, the number of cases continues to rise. Due to morbidity and premature deaths as well as its direct and indirect impacts on economic systems, cancer has placed a heavy burden on healthcare systems around the world.[1] Cancer is a very complicated sequence of disease conditions due to its multi-factorial nature. The interplay of genetics, lifestyle, physiological and environmental factors raise the challenge to provide reliable approaches for effective prevention, early detection, and providing reliable treatment strategies.[2,3] Among cancers, breast cancer is the most commonly diagnosed cancer worldwide, with significant repercussions on public health. The global burden of breast cancer is expected to rise in the future. According to epidemiological data, the rate of breast cancer may increase to reach 4.4 million cases by 2070.[4]

The most common strategies used to treat breast cancer are chemotherapy surgery and radiotherapy which remain invasive methods. The medical and technological advances as well as the understanding of the molecular pathways involved in cancer provided new advances in treatments.[5] This knowledge gave rise to the development of new treatment strategies such as immunotherapy and targeted medicines, providing more effective and individualized treatment choices for some cancer types.[5] Despite this progress, some cancer types increase in malignancy. Several factors could influence cancer's progression and treatment resistance mainly the tumor growth kinetics, the early age of diagnosis, and the degree of tumor's heterogeneity.[6]

Drug resistance is the main factor contributing to treatment failure in cancer. Amid the tumor heterogeneity, several drug resistances were noticed including all modes of therapy available including targeted therapy, immunotherapy in addition to conventional ones such as chemotherapy and radiotherapy.[7,8] This resistance was perceived across all cancer subtypes; therefore a particular emphasis was placed on the need to explore new alternative treatments.

Alternative treatments for cancer have made significant stride when conventional cancer treatments fail to provide sustainable and efficient therapy due to drug resistances and side effects.[9,10] A revival interest towards natural products as source of bioactive phyto compounds motivated researchers to implement new therapeutic strategies.[11]

Among the investigated natural products, a great concern has been given to honey due to its high nutritional value and medicinal properties reported since ancient time in folk medicine. Honey might be an intriguing option in this regard. The diversity of honey is significantly influenced not only by its floral origin, but also by botanical and geographical source. This diversity enriches the honey composition with potent properties to cure diseases mainly breast cancer.[12,13]

In this review, we report the findings obtained about honey investigation as well honey-based therapeutics in breast cancer considering the last reports from 2020 to 2024 referring to bibliographical data.

Honey-based therapeutics

Several studies have highlighted the effects of honey on several cancer types, namely breast cancer.[14] Since honey derives from plants, valuable phytochemicals or their derivatives will be found in honey content especially if it is derived from a medicinal plant. Moreover, the diversity of phyto compounds depends also on the nectar through which the honey is produced. This diversity is not only due to the variety of plants that produce nectar but also by the environmental and management conditions under which the nectar is harvested. Honey's composition, which includes a wide spectrum of phytochemicals with demonstrated antimicrobial, antioxidant, and anti-inflammatory properties, varies according to its origin. To date, over 200 constituent compounds have been identified.[12] Complementary therapy utilizing these natural items or their derivative phytochemicals could serve as a great alternative to overcome cancer burden and provide efficient treatments. Honey has been established as a potential therapeutic antioxidant agent for various diseases. Clinical studies have shown that honey could be an alternative treatment method, less toxic than conventional cancer treatments such as chemotherapy and radiation therapy (Figure 1).

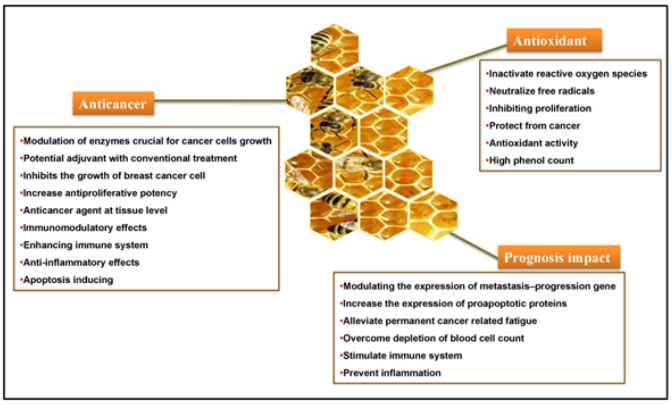

Figure 1 Honey-based therapeutics: anticancer, antioxidant, and prognostic impacts in breast cancer treatment.

Antioxidant potency

The high antioxidant content found in honey could reduce the chances of getting diseases associated with oxidative stress such as cancers, particularly breast cancer.[15] Honey's anticancer activity can be attributed to its rich and complex constituents including polyphenols, flavonoids as well as various kinds of sugars, phenolic acids, enzymes, amino acids and polypeptides. These compounds exhibit several anticancer mechanisms, including antiproliferative, immunomodulatory, and anti-inflammatory effects, apoptosis inducing and inhibition of the tumor necrosis factor.[16] Flavonoids and phenolic acids are among the most common phenolic compounds found in honey and are responsible for the prominent antioxidant potential. The ability of these compounds to inactivate reactive oxygen species (ROS) and neutralize free radicals generated during diverse cellular processes help reduce oxidative stress.[12,17]

Several studies have established a close correlation between total phenol count and the antioxidant potential. Several Asian *Kelulut* honey harvested from many areas displayed variable antioxidant potential in dose dependent manner related to the total phenol count.[18] We conclude that honey antioxidant potential is correlated to its phenol containing as well the geographical origin. This antioxidant potential could contribute to anticancer attributes displayed by several honey thereby inhibiting the proliferation of cancerous cells.[19] That was confirmed by Karbasi et al while comparing two variety of honey (*Ziziphus jujube* honey and commercial honey) by assessing the phenolic content, antioxidant capacity, and diastase activity and investigation the cytotoxic effect on MCF-7 breast cancer cell line. The conducted experiments unveiled that MCF-7 cells treatment with *Ziziphus jujube* honey may decrease significantly the migration rate in a dose-dependent manner and thus is mainly due to the highest phenolic content.[20]

Several studies have shown the complexity of polyphenol bioavailability, which is controlled by multiple in vivo factors; it has been outlined that polyphenols derived from honey are more available and could be maintained by repeated consumption to exhibit excellent antioxidant activity.[21] The daily uptake of honey may help to prevent cancer due to the valuable provided amount of antioxidant.

Anticancer potency

Honey has been studied for its potential anticancer attributes. It has shown some promising results in laboratory settings. Different varieties of honey, such as Manuka, Nigellasativa, Moringa, sidr, and Pumpkin honey, have been tested for their effects on human cancer cells and led to significant outcomes. The mechanism of action of honey on cancer cells involves several processes beside the antioxidant potential, likewise modulation of enzymes crucial for cancer cells growth, immunomodulatory effects by stimulating and enhancing immune system to recognize and eliminate cancer cells, anti-inflammatory effects by reducing inflammation which is a common factor in the development and progression of cancer and prevent their growth .[22–25]

Several research findings have emphasized the anticancer characteristics of honey, namely its potential effects on breast cancer. Studies investigating induced breast cancer in female Sprague dawley rats treated with crude honey revealed a positive potency of honey as an anticancer agent at tissue level.[26] Several Saudi honey displayed great anticancer potency mainly against breast cancer and were confirmed in vitro mainly Shaoka honey, Acacia honey, Sidr honey and Tamarix honey. [27–29]

Previous studies reported that Malaysian Acacia honey inhibits the growth of breast cancer cell line MCF-7 by apoptosis inducing after only 2 hours of treatment (IC_{50} 5.49 µg/mL) while the formation of the apoptotic bodies could be observed within 6 hours of treatment.[30] That finding was also confirmed in another study investigating Acacia honey derived from Saudi Arabia and prominent anticancer activity on the same MCF-7 cell line (IC_{50} 5.053 µg/mL) were noticed with apoptosis inducing essentially(Figure 2).[13] The in silico investigation of Acacia honey compounds disclosed that melezitose is among the most important potential bioactive compounds that could interact with apoptotic p53 protein to trigger apoptosis .[13]

Likewise the anticancer effects related to apoptosis inducing have been also demonstrated through its anti-estrogenic effects and its ability to trigger mitochondrial membrane depolarization and apoptosis in breast cancer cells.[31] The anti-estrogenic effects have been assigned to polyphenolic honey compounds mainly the Chrysin (5, 7-dihydroxyflavone) which is able to inhibit the aormatase cytochrome P450 enzyme that transform androgens to estrogens.[32] Consequently these shade new insights on hormone-dependent breast cancer treatments. Other findings highlight the impact of honey on apoptosis inducing by a significant modulation of apoptotic genes expression, mainly upregulation of Bax, p53 and p21 and down regulation of Bcl-2 genes.[20]

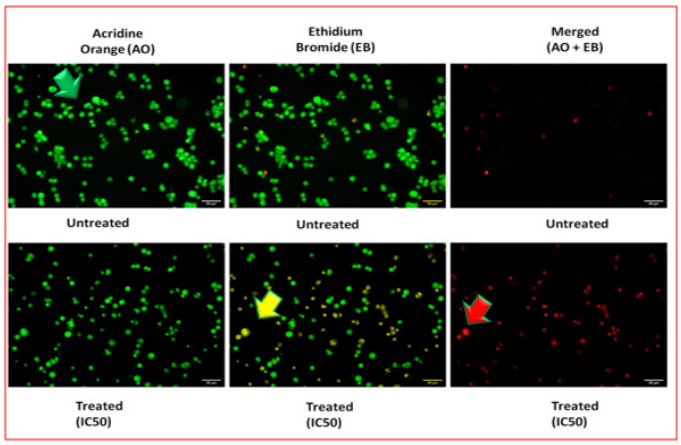

Figure 2 Determination of apoptosis inducing using fluorescent microscopy employing double staining method of MCF-7 Cells Treated with IC50 of Acacia honey, compared to untreated cells used as control.[13] (Note: Viable cells: green color (green arrow); Early apoptotic cells: yellow color (yellow arrow); Necrotic cells: red color (red arrow). Magnification: 100x).

An interesting study showed that Indian unifloral Ajwain honey displayed interesting in vitro cytotoxic activity on MDA-MB-231 breast cancer cell line.[33] MDA-MB-231 cell line is commonly used to model late-stage breast cancer, moreover the absence of growth factor receptor HER2 make of them good model to investigate triple-negative breast cancer which are associated with worse outcomes. The unifloral Ajwain honey displayed also great anti-inflammatory effect by inhibiting both metalloproteinases 2 and 9 proteins.[33] These two proteins are involved in collagen IV degrading that constitutes a significant component of extracellular matrix paving the way for tumor cell invasion.[33] Other findings unveiled that Tualang honey extract could exert an anticancer potential in dose dependent manner by reducing the viability of the tested breast cell lineage MCF-7.[34]

Several studies have demonstrated the in vitro anticancer potency of Tualang honey by inducing cell death and apoptosis in breast cancer cells.[35] All those findings highlight that crude honey could be used as an anticancer agent for breast cancer. Explorations revealed that the honey anti-proliferative potency could be increased up to 104 times with the nano encapsulation of honey extracts in micro emulsion formulations which leads to notable decrease in the IC_{50} values.[36] This efficiency could be mainly attributed to size of honey micro emulsion that could be better uptake by targeted cells. Furthermore, honey mediated green synthesis of nanoparticles expend horizons for new alternative therapeutics.[37,38] These findings exploring micro emulsion formulations and green synthesis of nanoparticles could give new insight to uncover new alternatives to treat breast cancer. The anticancer potency of honey could be either direct or indirect. Besides to its outstanding direct effects mainly due to its anticancer potency, honey could exhibit indirect healing properties. Experiments consisting of the supplementation of probiotics with Lime honey or Chestnut honey revealed a higher targeted impact on breast cancer without affecting healthy cells.[39,40] Moreover clinical investigations demonstrate that honey compounds could be used as potential adjuvant with conventional treatments to assure better healing efficiency and to enhance outcomes.[14]

Prognosis impact

Recent studies on animal models revealed the potential use of honey in cancer prevention and treatment.[41] Alongside the healing properties, a prognostic interest has been highlighted in breast cancer patients who underwent chemotherapy. Since chemotherapy leads to a depletion of blood cell count, it has been proven that Dorsata honey supplementation increases hematopoietic growth factor Interleukin-3 to overcome the deficiency.[42] Moreover, Api dorsata honey could improve prognosis in breast cancer patients by stimulating the immune system to increase the T lymphocyte levels which may suppress the development of tumor cells as well increasing the interleukin 37 which is associated to protective effect on breast cancer.[43]

In addition to polyphenols, an insight has been given to honey sugars for their modulating effects on breast cancer cells. The assay consists of the administration of honey sugars analogue (fructose, glucose, maltose, and sucrose) in breast cancer-induced albino Sprague–Dawley rat model. They concluded that honey sugars analogue could increase the expression of proapoptotic proteins while reducing anti-apoptotic proteins expression.[44] It has been proven also that Sidr and wild honey could improve breast cancer treatment through modulating the expression of metastasis–progression gene on a human breast adenocarcinoma MDA-MB-231 cell line.[45] This would emphasize the use of honey as adjuvant in breast cancer treatment. It has been substantiated that honey could be a great alternative to alleviate permanent cancer-related fatigue in breast cancer patients receiving chemo-radiation treatments.[43,46] Another study outlines the protective effect of Multiflora honey from hepatotoxicity related to chemotherapy in invasive ductal breast cancer patients.[47]

This hepatoprotective effect could improve prognosis and enhance patient's life quality. Similarly, observations unveiled that Tualang honey supplementation at 20g/day could prevent inflammation in postmenopausal breast cancer patients.[35] A clinical trial disclosed that Thyme honey oral gel could be used as a prophylactic agent to decrease the severity of the symptoms of Oral mucositis which is a common complication associated to chemotherapy cancer treatment.[48] One more investigational study revealed that honey-lime spray may be a good alternative to treat xerostomia syndrome (dry mouth) which is a common side effect frequently experienced by cancer patients undergoing chemotherapy.[49]

Conclusion

In conclusion, honey-based therapeutics unveil new insights for valuable alternative treatments for breast cancer. Honey's anticancer properties, antioxidant potency, and its potential prognosis impact in breast cancer warrant further investigation. Due to the intricate honey composition and the lack of comprehensive understanding regarding its constituent phytochemicals and their specific mechanisms of action. This lack of knowledge explains why honey's application in conventional medicine is restricted, especially without a standardized measure of its biological activities. Consequently, additional research is necessary to identify and analyze each compound, aiming to enhance our understanding of the underlying mechanisms of action.

While more research is needed to fully understand its mechanisms and establish optimal dosing regimens, honey represents a promising complementary therapy that could enhance the effectiveness of conventional breast cancer treatments.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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