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REVIEW ARTICLE

# Chemotherapeutic Potentials of Honey in Cancer Management: A Prospect for Integrative Oncology

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## ABSTRACT

Honey has attracted increasing interest as a natural adjunctive agent in integrative oncology because of its diverse bioactive constituents and potential effects on cancer-related cellular mechanisms. This review synthesized evidence on the anticancer properties of honey, including its mechanisms of action, effects in different cancer models, and possible supportive role alongside conventional cancer therapies. A literature search was conducted in PubMed/MEDLINE and Google Scholar from database inception to December 2025, supplemented by manual searching of reference lists. Search terms included combinations such as "honey AND cancer," "Manuka honey AND apoptosis," and "honey AND chemotherapy." Eligible studies included in vitro, animal, and clinical investigations assessing whole honey of any botanical origin in cancer models. Non-English articles and studies focusing on other bee products were excluded. After duplicate removal and stepwise screening, 107 studies were included in the qualitative synthesis. Evidence suggests that honey may inhibit tumor cell proliferation through prooxidant and pro-apoptotic effects, enhance immune responses by modulating macrophages, T lymphocytes, natural killer cells, and cytokines such as TNF-α, IL-1, and IL-6, and suppress inflammatory pathways including COX-2. Honey may also influence estrogen receptor signaling in breast cancer. In addition, it has shown potential in reducing chemotherapy-induced complications such as oral mucositis, nephrotoxicity, hepatotoxicity, and suppressed hematopoiesis. Overall, honey appears promising as a supportive adjunct in oncology, but larger randomized clinical trials are needed to standardize preparations, determine optimal dosing and administration routes, and clarify molecular targets in humans.

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## 1. INTRODUCTION

The exploration of effective strategies for cancer management has fostered an increasing interest in natural products, with honey being particularly significant due to its historical application for medicinal purposes over centuries (Usman et al., 2025). Modern research has progressively illuminated honey's potential as an adjunctive therapeutic agent in oncological treatment. This may primarily be due to its bioactive constituents that exhibit anticancer properties. Particularly, Manuka honey has received considerable attention for its unique composition and therapeutic benefits (Porcza et al., 2016; Sharaf El-Din et al., 2025). Investigations indicate that honey encompasses a range of mechanisms of action that may substantiate its anticancer effects. These mechanisms include anti-proliferative, pro-apoptotic, anti-inflammatory, and antioxidant activities (Kiryowa et al., 2025). For instance, empirical studies have demonstrated that honey can induce apoptosis in malignant cells while safeguarding normal cellular integrity. This suggests a selective cytotoxicity that could enhance treatment efficacy without the significant adverse effects commonly associated with conventional chemotherapeutic approaches.

Furthermore, honey's ability to modulate critical signaling pathways involved in tumorigenesis and cancer cell survival has been documented. These include AMPK/AKT/mTOR and STAT3 pathways (Talebi et al., 2020). This showed its potential roles in inhibiting cancer cell proliferation and metastasis. The strategic application of honey in the management of oncological conditions is notably pertinent within the context of hormone-sensitive neoplasms, notably illustrated by estrogen receptor-positive breast carcinoma (Kwon et al., 2022). Preliminary research conducted using animal models suggests that Manuka honey possesses the capacity to significantly inhibit tumor proliferation by up to 84% in murine studies (Márquez-Garbán et al., 2024). This substantiates its potential as a natural complement or alternative to conventional cytotoxic medications.

Additionally, the rich array of phenolic compounds found in honey has been associated with improved therapeutic outcomes when co-administered with chemotherapeutic agents. As a result, honey may potentially curtail certain limitations like pharmacological resistance and the debilitating contraindications associated with conventional cytotoxic drugs (Honarbakhsh et al., 2026). The contributions of honey extend beyond simple direct antineoplastic properties. Interestingly, it has been documented to alleviate chemotherapy-induced complications (Nurhidayah et al., 2024a). The key mechanism is by promoting tissue regeneration and reducing inflammatory responses. This bifunctional capability not only improves the quality of life for patients but also underscores the importance of integrating natural products into comprehensive cancer care frameworks (Anshasi et al., 2025). Moreover, honey supplementation has been shown to stimulate hematopoiesis by increasing interleukin-3 levels and boosting immune cell functions (Safitri et al., 2024). Importantly, this may neutralize the deleterious effects of cancer chemotherapy on blood cell depletion and improve patient prognosis (Eteraf-Oskouei & Najafi, 2022). In this review of existing literature, we sought to synthesize current evidence supporting honey's role in cancer prevention, therapy enhancement, and symptom management. The review highlighted the potential of honey as a novel natural, complementary therapeutic agent in integrative oncology.

## 2. SEARCH STRATEGY

A comprehensive literature search was conducted using PubMed/MEDLINE and Google Scholar, complemented by manual hand-searching of reference lists of relevant articles to identify additional eligible studies. The search covered studies published from database inception to December 2025. Example search strings included: "honey AND cancer", "Manuka honey AND apoptosis", "honey AND chemotherapy", "honey AND oral mucositis", and "honey AND breast cancer". Boolean operators (AND, OR) were applied to refine results. Only articles published in English were considered. Eligible studies included in vitro experiments, animal studies, observational studies, and clinical trials that evaluated whole honey (any botanical origin, including but not limited to Manuka, Tualang, Sidr, Gelam, thyme, and other monofloral or multifloral varieties) in any cancer type. Studies focusing exclusively on isolated bee products (e.g., propolis or bee venom), non-oncologic conditions, review articles, conference abstracts without full text, duplicate publications, and non-English papers were excluded.

All retrieved records were screened in a stepwise manner. Titles and abstracts were first assessed for relevance to honey and cancer-related outcomes. Potentially eligible articles underwent full-text review to confirm compliance with inclusion criteria. Duplicates identified across databases were removed prior to screening. Studies that did not clearly report cancer models, anticancer mechanisms, adjunctive chemotherapy effects, or clinical outcomes were excluded at the full-text stage. Screening and eligibility assessment continued iteratively until a final total of 107 studies met the predefined inclusion criteria and were included in this review (Figure 1).

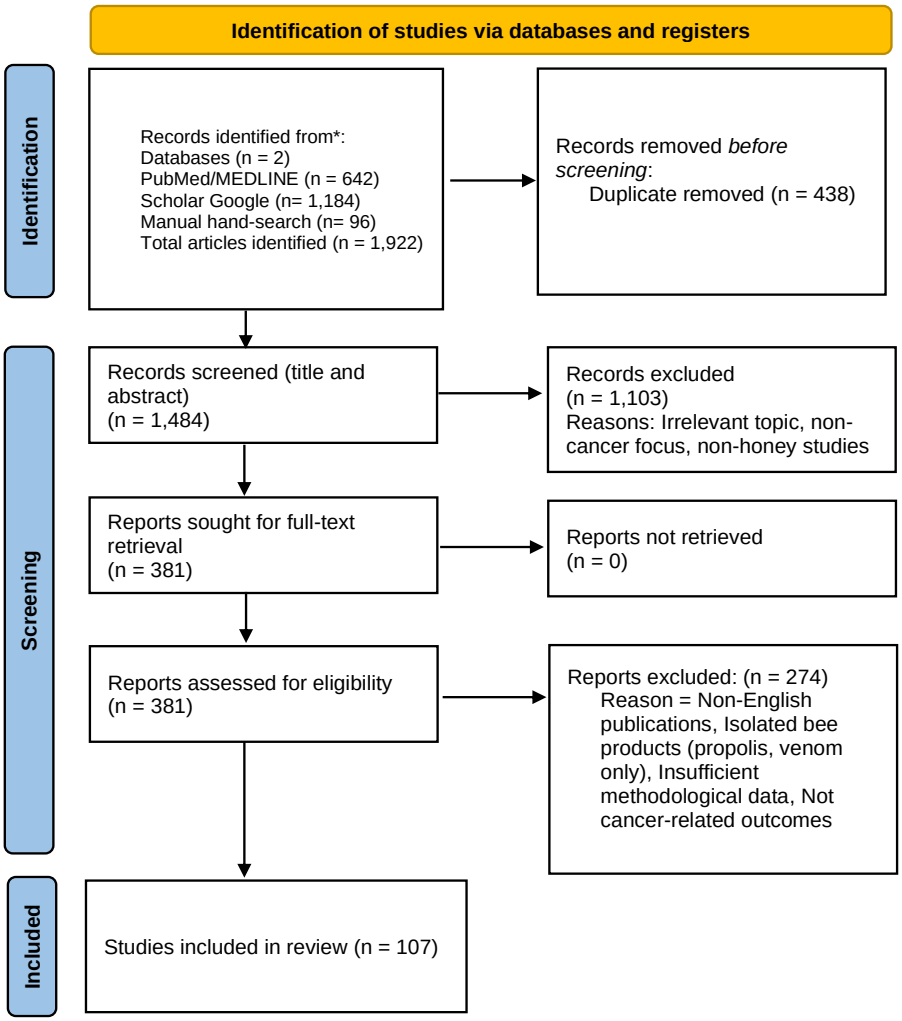


**Fig 1:** PRISMA Flow diagram

### 3.1 OVERVIEW OF CANCER AND ITS IMPACTS

Cancer is a complex and multifaceted disease characterized by the uncontrolled growth and proliferation of abnormal cells, which can invade surrounding tissues and metastasize to distant organs, leading to significant morbidity and mortality worldwide (Brown et al., 2023). According to the World Health Organization, cancer accounted for nearly 10 million deaths globally in 2020, making it one of the leading causes of death, with common types including breast, lung, colorectal, and prostate cancers (Bray et al., 2024). The disease arises from a series of genetic mutations that disrupt normal cellular processes. It may be triggered by a combination of environmental factors (like exposure to carcinogens), lifestyle choices (such as tobacco use and poor diet), and genetic predispositions (Sandhu et al., 2024). The progression of cancer typically involves the initiation, promotion, and progression stages (S. Zhang et al., 2024).

The impact of cancer extends beyond physical health. Regrettably, it poses significant psychological, social, and economic challenges for patients and their families. Patients often experience emotional distress, anxiety, and depression due to the diagnosis and treatment processes (Shalata et al., 2024). This can adversely impact the financial status due to medical expenses. Moreover, disparities in cancer care exist globally. In fact, high-income countries have better access to comprehensive treatment options relative to low- and middle-income countries, where less than 15% of patients may receive adequate care (dos-Santos-Silva et al., 2022). This makes the quest for effective natural products as complements or alternatives inevitable. The side effects associated with standard treatments such as chemotherapy and radiotherapy can further complicate patient outcomes. This highlights the need for innovative therapeutic approaches that minimize toxicity while maximizing

efficacy (Majeed & Gupta, 2025). The biochemical foundations of oncogenesis are intricately rooted in a series of genetic and molecular modifications that instigate the uncontrolled proliferation of cells, ultimately leading to tumor formation and progression. At the genetic level, oncogenes, which are the mutated forms of proto-oncogenes, play a crucial role by promoting cellular growth and division (Dakal et al., 2024). Notable examples include the RAS gene, which is associated with signaling pathways that regulate cellular proliferation (Bahar et al., 2023). Another example are the HER2 and the HER3 genes, which are often amplified in certain subtypes of breast cancer (Majumder et al., 2021). Unfortunately, mutations in these oncogenes trigger the aberrant activation of pathways that may facilitate tumorigenesis (Galiè, 2019). Conversely, tumor suppressor genes such as TP53, BRCA1, and BRCA2 typically function to impede cellular division or promote apoptosis (Quaas et al., 2026). Meanwhile, the TP53 gene, which encodes the p53 protein, is particularly critical as it maintains genomic stability and regulates the cell cycle (Alsulami, 2025). Importantly, mutations affecting p53 are found in approximately fifty percent of all cancers (Wang et al., 2025). This allows for the survival and unregulated proliferation of cells with damaged DNA. Moreover, genes involved in DNA repair are essential for rectifying DNA damage. The mutations in these genes may result in the accumulation of genetic irregularities that contribute to cancer pathogenesis by increasing the likelihood of subsequent mutations in both oncogenes and tumor suppressor genes (Borrero & El-Deiry, 2021). Biochemically, malignant cells exhibit deregulated cell cycle control due to alterations in proteins such as cyclins and cyclin-dependent kinases (CDKs) (Pellarin et al., 2025). Consequently, this may exacerbate unrestrained cellular division. Furthermore, cancer cells often evade programmed cell death (apoptosis) through mechanisms such as the overexpression of anti-apoptotic proteins like Bcl-2 (Milletti et al., 2023). The preservation of telomeres represents another vital component. Importantly, many cancer cells may activate telomerase activity. Consequently, this allows the cancer cells to extend telomeres and attain a condition of limitless replicative capacity (Robinson & Schiemann, 2022). Additionally, cancer cells typically display a reconfigured metabolic profile characterized by the Warburg effect, whereby they preferentially utilize glycolysis for ATP production even in the presence of oxygen (Jacquet & Stéphanou, 2025). This metabolic shift supports enhanced proliferation and survival under hypoxic conditions that are often encountered within the tumor microenvironment (Liberti & Locasale, 2016).

### 3.2 Honey as a natural supplement

. Honey constitutes a complex and naturally occurring substance produced by Apis mellifera through the transformation of nectar sourced from angiosperms (Almasaudi, 2021). It is characterized by its high sugar concentration, primarily composed of fructose and glucose, which together account for approximately 75% of its total composition (Sharaf El-Din et al., 2025). Honey is a unique master mix of over 200 distinct compounds, including enzymes, vitamins, essential minerals, organic acids, and a diverse range of phytochemicals that collectively contribute to its alleged health-promoting properties (Eteraf-Oskouei & Najafi, 2013). The biosynthetic process involves the collection of nectar by bees, which subsequently undergoes enzymatic transformation and evaporation within the hive (Na et al., 2024). Subsequently, this may result in a viscous fluid distinguished by a diminished water content. Accordingly, the regulated moisture content confers effective antimicrobial properties, thereby endowing honey with remarkable shelf life (Adeoye et al., 2022a). Honey is revered not only for its sweetening attributes but also for its therapeutic properties. It has been utilized in traditional medicinal practices for millennia to treat a variety of health issues, ranging from cutaneous injuries and burns to respiratory disorders and gastrointestinal disturbances (Nicolson et al., 2022).

Contemporary scientific investigations have increasingly concentrated on the prospective anticancer attributes of honey, elucidating its antioxidative, anti-inflammatory, and immune-modulatory effects that may augment the efficacy of standard oncological treatments while mitigating associated adverse reactions (Masad et al., 2021). For instance, empirical studies have demonstrated that honey can promote apoptosis in neoplastic cells, impede tumor proliferation, and modulate critical signaling cascades implicated in carcinogenesis (Kmail, 2026). Varieties such as Manuka honey are particularly distinguished for their elevated concentrations of methylglyoxal and phenolic acids, which significantly contribute to these beneficial effects (Martinotti et al., 2024). Notwithstanding the encouraging evidence regarding honey's health-promoting properties, challenges stemming from compositional variability influenced by floral sources and geographic conditions necessitate further scholarly inquiry aimed at standardizing its application in clinical environments (Ayoub et al., 2023).

### 3.3 Pro-oxidant and pro-apoptotic potentials of honey in cancer models

Honey is a rich repository of essential nutrient classes such as phenolic compounds, flavonoids, terpenoids, vitamins, sugars, and enzymes. These have been demonstrated to play a pivotal role in modulating oxidative stress and apoptosis in human pathologies (Adeoye et al., 2022b). Whereas, honey is well reputed for its antioxidant functions in healthy cells and some human diseases, it elicits a pro-oxidant effect in highly proliferating cells. Empirical evidence showed that honey induces the expression of glutathione-encoding genes in clinical isolates of *Pseudomonas aeruginosa* (Adeniji et al., 2025). Notably, honey has been shown to curtail tumorigenesis in several cancer models by downregulating the activities of intrinsic antioxidant enzymes (as reviewed by Erejuwa et al., 2014).

Honey's capacity to modulate oxidative stress has been evidenced in colon cancer models. Specifically, varying manuka honey doses (8, 16 and 24 mg/mL) were reported to exert a pro-apoptotic effect in human HCT-116 colon cancer cell lines by elevating intracellular ROS levels (Cianciosi et al., 2020). In another study, manuka honey modulated intracellular ROS levels, leading to apoptosis in A431 cell lines by upregulating $H_2O_2$ permeability through aquaporin-3 (Martinotti et al., 2020). Also, co-administration of manuka honey with 5-fluorouracyl elicited selective cytotoxicity by modulating ROS and apoptotic signaling in human HCT-116 cell lines (Afrin et al., 2018). In addition, there was selective induction of apoptosis in triple-negative MDA-MB-231 and estrogen receptor-positive MCF-7 breast cancer cell lines when exposed to varying doses of manuka honey below 2.5% w/v. Furthermore, Pervari Honey from Turkey significantly modulated ROS levels, eliciting oxidative DNA damage, and apoptosis rate in MCF-7 and MDA-MB-231 breast cancer cell lines (Derya Andeden et al., 2024). Moreover, *Arbutus unedo* honey induced a higher level of ROS in metastatic (LoVo) cell lines, compared to manuka honey (Afrin et al., 2017). Distinctively, Yee et al., (2022) demonstrated that Sangju honey increased the expressions of p21, p53, cleaved caspase 3, and caspase 9, thereby inducing apoptosis in human oral squamous cell carcinoma (OSCC) at 0.25% and 0.5% concentrations. These pieces of evidence showed that the selective pro-apoptotic effects of honey seemed to be elicited through the induction of mitochondrial depolarization and the selective activation of caspases in cancerous cells, but not in healthy cells.

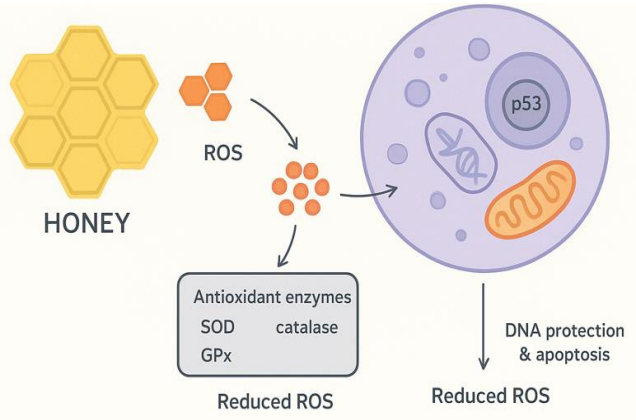


**Fig 2:** Mechanisms of antioxidative action of honey in cancer models

This schematic (**Figure. 2**) provides a conceptual summary of the antioxidative and pro-apoptotic mechanisms attributed to honey and its bioactive compounds, as reported in preclinical studies

### 3.4 Modulatory properties of honey on inflammation and immune signalling in cancer models

Chronic inflammation is a pivotal factor in the etiology and progression of cancer. The prominent inflammatory mediators in cancer include tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6), and cyclooxygenase-2 (COX-2) (Nishida & Andoh, 2025). These play critical roles in fostering tumor initiation, proliferation, and metastasis. The anti-inflammatory properties of honey are largely ascribed to its abundant array of distinctive bioactive constituents (Badolato et al., 2017). These encompasses phenolic acids, flavonoids, and enzymes that synergizes to modulate inflammatory pathways frequently disrupted in malignancies (Waheed et al., 2019). Empirical evidence suggests that honey possesses the capacity to inhibit the activation of nuclear factor kappa B (NF-kB) and mitogen-activated protein kinase (MAPK) signaling cascades (Das et al., 2022).

The bioactive components of honey, encompassing flavonoids and phenolic acids, play a crucial role in orchestrating immune responses and augmenting the organism's ability to combat tumorigenesis (Porcza et al., 2016). Empirical investigations indicate that honey can enhance the production of pivotal immune cells, including macrophages, T lymphocytes, and natural killer (NK) cells , thereby bolstering the overall immune response against neoplastic cells (Ahmed & Othman, 2013). Research has demonstrated that honey promotes the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, which are vital for modulating immune responses and apoptosis in cancerous cells (Masad et al., 2022). In vitro studies have revealed that honey can amplify the cytotoxic effectiveness of NK cells against a range of cancer cell lines, including breast and colorectal malignancies, by enhancing the expression of activation markers on these immune effector cells (Navaei-Alipour et al., 2021).

Furthermore, honey's capacity to inhibit the activation of NF-kB and MAPK signaling pathways may results in a reduction of inflammatory mediators and pro-inflammatory cytokines linked to tumor progression (Masad et al., 2021) For instance, gelam honey has been documented to attenuate NF-kB activity in transformed cell lines, leading to a decrease in inflammation and tumor proliferation (Tlak Gajger et al., 2025). This highlights its prospective role as an adjunctive therapeutic agent in oncological treatment.

### 3.5 Effect of honey on estrogenic activities

Research findings indicate that honey may exert a biphasic effect on estrogen receptor (ER) activity, acting as both an estrogen agonist and antagonist (Rahmani & Babiker, 2025). For example, studies have shown that at lower concentrations (0.2–5 µg/mL), honey extracts can inhibit the proliferation of estrogen-responsive MCF-7 breast cancer cells by counteracting the effects of estradiol. Whereas, at higher concentrations (20–100 µg/mL), honey may exhibit estrogenic properties that promote cell growth (Henderson et al., 2016). This dual functionality is ascribed to the phenolic compounds present in honey, which possess the ability to modulate ER signaling pathways (Martiniakova et al., 2023). In an investigation, extracts obtained from Greek thyme and pine honey were found to negate estrogen

activity in the presence of estradiol, indicating their potential role in the management of estrogen-driven tumor proliferation (Tsiapara et al., 2009), Moreover, the presence of flavonoids such as quercetin and chrysin in honey has been associated with the modulation of ER activity (Ismail et al., 2021). These bioactive compounds can influence gene expression linked to cell proliferation and apoptosis in breast cancer cells. For instance, chrysin has been shown to inhibit the proliferation of MCF-7 cells by modifying the expression of genes relevant to the cell cycle and apoptosis pathways (Tsiapara et al., 2009). Additionally, honey's ability to reduce levels of pro-inflammatory cytokines and inhibit cyclooxygenase-2 (COX-2) further corroborates its role in modulating estrogenic effects, given that chronic inflammation is acknowledged to exacerbate estrogen-related tumorigenesis (Ranneh et al., 2021). In preclinical models, the application of honey has resulted in significant reductions in tumor volume and growth rates in ER-positive breast cancer models (Márquez-Garbán et al., 2024). This suggests that honey may serve as a complementary therapeutic agent by modulating estrogen signaling pathways and reducing reliance on conventional hormonal therapies. Different types of honey with their bioactive, anti-cancer mechanisms and cancer models are summarized in **Table 1.**

**Table 1:** Types of honey with their bioactive, anti-cancer mechanisms and cancer models

| # | Honey Variety | Bioactive Component(s) | Anticancer Mechanisms | Cancer Models Studied | Reference |
|---|---|---|---|---|---|
| 1 | Manuka Honey | Methylglyoxal, flavonoids (quercetin, kaempferol) | Associated with pro-apoptotic and antiproliferative effects in preclinical models | MCF-7 (breast), A375 (melanoma) | (Márquez-Garbán et al., 2024) |
| 2 | Tualang Honey | Flavonoids (chrysin, luteolin), phenolic acids | Reported to exhibit antioxidant activity and potential apoptosis-inducing effects | HCT-116 (colon), MCF-7 (breast) | (Erejuwa et al., 2014) |
| 3 | Buckwheat Honey | Quercetin, caffeic acid | Associated with antiproliferative and pro-apoptotic effects | PC-3 (prostate), Caco-2 (colon) | (Porcza et al., 2016) |
| 4 | Sidr Honey | Flavonoids, phenolic compounds | Reported antioxidant and anti-inflammatory properties | HepG2 (liver), A549 (lung) | (Ghramh et al., 2023) |
| 5 | Kelulut Honey | Phenolic acids, flavonoids | May modulate signalling pathways and inhibit cell proliferation | MCF-7 (breast) | (Al-Kafaween et al., 2023) |
| 6 | Acacia Honey | Gallic acid, flavonoids | Primarily reported antioxidant activity with potential anticancer relevance | HeLa (cervical), HL-60 (leukemia) | (Afrin et al., 2020) |
| 7 | Gelam Honey | Flavonoids (apigenin), phenolic acids | Associated with cell cycle modulation in cancer cells | MCF-7 (breast) | (Yusof et al., 2021) |
| 8 | Chestnut Honey | Caffeic acid, quercetin | Reported antiproliferative activity in cancer models | A375 (melanoma), HCT-116 (colon) | (Jaganathan & Mandal, 2009) |
| 9 | Fir Honey | Flavonoids | Reported biphasic estrogenic activity in breast cancer models | MCF-7 (breast) | (Tsiapara et al., 2009) |
| 10 | Greek Thyme Honey | Phenolic compounds | Reported antioxidant and anti-inflammatory effects | MCF-7 (breast) | (Spilioti et al., 2014) |
| 11 | Pine Honey | Flavonoids | Associated with modulation of estrogen-related activity | MCF-7 (breast) | (Erejuwa et al., 2014) |

| | | | | | |
|---|---|---|---|---|---|
| 12 | Rosemary Honey | Kaempferol | Associated with antiproliferative and pro-apoptotic effects | A375 (melanoma) | (Afrin et al., 2020) |
| 13 | Sunflower Honey | Quercetin | Reported antiproliferative activity | HL-60 (leukemia), Caco-2 (colon) | (Jaganathan & Mandal, 2009) |
| 14 | Clover Honey | Flavonoids | Reported antioxidant activity and potential modulation of cellular pathways | Various cancer cell lines | (Erejuwa et al., 2014) |
| 15 | Eucalyptus Honey | Phenolic compounds | Reported antioxidant and anti-inflammatory properties | HCT-116 (colon), A549 (lung) | (Wang, 2020) |

### 3.6 Effect of honey Co-Administration with cytotoxic drugs

The simultaneous utilization of honey alongside standard chemotherapeutic agents has garnered substantial scholarly attention in recent years. This therapeutic potentials can be attributed to its ability to enhance the efficacy of oncological interventions while mitigating the adverse effects commonly associated with chemotherapy (Bose et al., 2024). Empirical data indicate that honey, Manuka honey, possesses the capability to sensitize neoplastic cells to chemotherapeutic agents, thus facilitating the administration of lower dosages and reducing toxicity. A specific study investigating the synergistic relationships between honey and cisplatin revealed that honey not only increased the vulnerability of cancer cells to the drug but also reduced the required dosage of cisplatin, thereby alleviating its debilitating nephrotoxic repercussions (Martinotti et al., 2024). Additionally, Tualang honey combined with tamoxifen demonstrated improved anticancer activity and reduced drug dose requirements in experimental models, supporting its use to mitigate side effects while enhancing therapeutic efficacy (Yaacob et al., 2013). Furthermore, combined supplementation of honey with natural agents such as *Aloe vera* synergistically promoted tumor cell apoptosis in experimental cancer models (Tomasin et al., 2024).

Furthermore, honey has demonstrated an ability to enhance the immune response during chemotherapy (Zhang et al., 2022). For instance, honey supplementation may elevate immunoglobulin levels and activate macrophages, which may contribute to tumor elimination (Chan-Zapata & Segura-Campos, 2021). This protective mechanism may be ascribed to the antioxidative properties of honey, which aid in diminishing oxidative stress induced by chemotherapy.

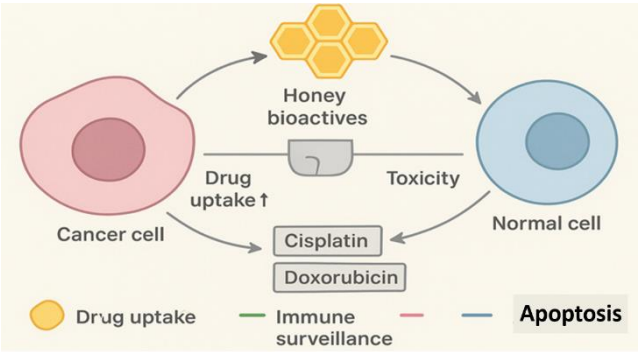


**Fig. 3 Synergistic interactions between honey and chemotherapeutic agents.** .

This schematic (**Figure. 3**) provides a conceptual overview of the potential interactions between honey and chemotherapeutic agents (e.g., cisplatin and doxorubicin), based largely on preclinical evidence. Honey may enhance anticancer activity through modulation of oxidative stress and apoptosis, and may reduce chemotherapy-induced toxicity via antioxidant and immunomodulatory effects. Further clinical validation is required.

### 3.7 Clinical outcomes of honey supplementation in cancer models

Clinical evidence demonstrates that honey supplementation confers multiple beneficial outcomes for cancer patients. Certain clinical studies have focused on breast cancer patients undergoing chemotherapy. In an intervention study among 30 post-chemotherapeutic breast cancer subjects, oral supplementation with *Apis dorsata* honey (5mL three times daily) for 15 days significantly increased T lymphocyte counts (Syam et al., 2021). This indicates enhanced cellular immunity that may potentially suppress tumor progression.

Interleukin-3 (IL-3) is a hematopoietic growth factor that is critical for blood cell formation (Podolska et al., 2024). Notably, IL-3 depletion is a distinct marker of myelosuppression in subjects undergoing cancer chemotherapy (Aliazis et al., 2024). In an intervention study,

supplementation with 15mL of *Apis dorsata* honey for 15 days significantly increased interleukin-3 (IL-3) levels among 30 breast cancer patients who underwent chemotherapy (Kurniawan et al., 2020). These findings underline honey's ability to potentially support hematopoiesis and immune recovery in oncology settings. Moreover, Tualang honey, have been evaluated in clinical contexts for antioxidative and organ-protective benefits. In postmenopausal breast cancer patients, Tualang honey supplementation (20 g/day for 12 weeks) significantly improved blood parameters and reduced hepatotoxicity markers (Zakaria et al., 2018). Meanwhile, oral mucositis (OM) may present as a painful inflammation and ulceration of the oral mucosa that compromises nutrition and quality of life (Shetty et al., 2022). Beyond immune enhancement, honey has shown efficacy in reducing the severity of chemotherapy- and radiotherapy-induced (OM) placebo (Co et al., 2016; Li et al., 2024). In a randomized controlled trial (RCTs) among 72 subjects with head and neck malignancies, the subjects in the intervention group, administered with thyme honey for 7 weeks, were graded lower in the overall assessment of oral mucositis relative to the control group (Charalambous et al., 2018). In addition, supplementation with thyme honey significantly improved the quality of life for patients in the intervention group. In a pilot quasi-experiment among 24 pediatric subjects with chemotherapy-induced mucositis, topical application of honey (three times daily) for five days elicited a significant reduction of the average mucositis score relative to the control (Nurhidayah et al., 2024).

In a quasi-experiment among 76 pediatric subjects with chemotherapy-induced oral mucositis, topical honey application significantly reduced the severity and treatment duration of the condition (Kobya Bulut & Güdücü Tüfekci, 2016). Similar observations were reproduced in an observational, blinded study among 100 children undergoing chemotherapy (Singh et al., 2019). In fact, the remarkable analgesic effect of honey in relieving the course of radiation induced nociception among cancer patients has been reviewed (Hao et al., 2022; Chu, 2024; Wishi et al., 2025). In a randomized phase II clinical trial among lung cancer subjects undergoing chemotherapy and radiotherapy, concomitant administration of 10mL liquid Manuka (4 times daily) for four weeks yielded a significant positive outcome with respect to opioid use (Fogh et al., 2017). These therapeutic effects are largely attributed to honey's antioxidant, anti-inflammatory, and antimicrobial properties. In a double-blinded, randomized controlled clinical trial among acute myeloid leukemia patients undergoing chemotherapy, one-month supplementation with honey and a honey-based product significantly reduced white blood cell count, gastrointestinal complications, and fever duration (Ebrahimi et al., 2016)

### Challenges, Limitations and Future Perspective

Notwithstanding the persuasive evidence endorsing the anticancer properties of honey, particularly concerning its role in enhancing the efficacy of conventional therapies and alleviating adverse effects, numerous challenges and limitations persist that warrant attention to fully realize its potential within the domain of clinical oncology. A primary challenge lies in the variability in the composition and quality of honey, which can significantly affect its biological activity. Factors such as the floral source, geographical provenance, and processing methods contribute to this variability, thereby complicating efforts toward standardization (Martinotti et al., 2024). For instance, although Manuka honey has been extensively researched for its unique antibacterial and anticancer properties, other honey varieties may not exhibit comparable effects due to differences in the concentrations of bioactive constituents such as flavonoids and phenolic acids (Johnston et al., 2018).

Moreover, the pathways through which honey exerts its anticancer properties remain insufficiently explored, underscoring the imperative for more thorough molecular research to elucidate these mechanisms. In addition, although preclinical investigations have produced promising results in vitro and in animal models, there exists a significant lack of rigorous clinical trials to validate these observations in human cohorts; the majority of existing studies are hampered by small sample sizes or inadequate methodological rigor (Martinotti et al., 2024). Another limitation is the possibility of interactions between honey and conventional chemotherapeutic agents that may affect drug metabolism or therapeutic effectiveness; understanding these interactions is crucial for the development of safe co-administration guidelines. Future research should emphasize the implementation of large-scale clinical trials to assess the efficacy and safety of honey as an adjunctive therapy in oncological treatment, alongside the exploration of novel formulations such as nano-encapsulation to enhance the bioavailability and targeted delivery of honey's bioactive components (Zayed Mohamed et al., 2019)

## CONCLUSION

Current evidence suggests that honey exhibits multiple biological activities relevant to cancer management, including antioxidant, anti-inflammatory, and immunomodulatory effects. A substantial proportion of the available data, primarily derived from in vitro and animal studies, indicates that honey and its bioactive constituents may inhibit tumor cell proliferation and induce apoptosis across various cancer models, including breast, liver, and colorectal cancers. These effects are largely attributed to its rich composition of phenolic compounds and flavonoids.

Notably, certain honey varieties, such as Manuka and Gelam honey, have demonstrated selective cytotoxic effects in preclinical studies, while sparing normal cells. In addition, emerging clinical evidence suggests that honey may help alleviate chemotherapy-related adverse effects, such as oral mucositis, thereby potentially improving patient quality of

life. Furthermore, its immunomodulatory properties may support host defense mechanisms during cancer treatment.

However, despite these promising findings, the current body of evidence remains limited by a scarcity of large-scale, well-designed clinical trials. Therefore, honey and its bioactive compounds should be regarded as potential adjunctive or supportive agents in integrative oncology rather than established therapeutic interventions. Further rigorous clinical studies are required to validate efficacy, determine optimal dosing, and clarify mechanisms of action in human populations.

## LIST OF ABBREVIATION

**AMPK** – AMP-Activated Protein Kinase
**AKT** – Protein Kinase B (PKB)
**ATP** – Adenosine Triphosphate
**Bax** – Bcl-2-Associated X Protein
**Bcl-2** – B-Cell Lymphoma 2
**BRCA1** – Breast Cancer Gene 1
**BRCA2** – Breast Cancer Gene 2
**CDKs** – Cyclin-Dependent Kinases
**COX-2** – Cyclooxygenase-2
**DNA** – Deoxyribonucleic Acid
**ER** – Estrogen Receptor
**GPx** – Glutathione Peroxidase
**HER2** – Human Epidermal Growth Factor Receptor 2
**IL-1** – Interleukin-1
**IL-3** – Interleukin-3
**IL-6** – Interleukin-6
**MAPK** – Mitogen-Activated Protein Kinase
**mTOR** – Mechanistic Target of Rapamycin
**NF-kB** – Nuclear Factor Kappa B
**NK cells** – Natural Killer Cells
**OM** – Oral Mucositis
**RCTs** – Randomized Controlled Trials
**ROS** – Reactive Oxygen Species
**SOD** – Superoxide Dismutase
**STAT3** – Signal Transducer and Activator of Transcription 3
**TNF-α** – Tumor Necrosis Factor-Alpha
**TP53** – Tumor Protein 53 (p53 gene)

## ETHICS STATEMENT

Not applicable. This study did not involve human participants, animal experiments, or clinical trials.

## DATA AVAILABILITY

No new datasets were generated in this review.

## CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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