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The anticarcinogenic properties of manuka honey - a literature review

1. **Adrianna Muciek [AM]**

The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow: Cracow, Malopolska, PL

https://orcid.org/0009-0002-5678-3780

e-mail: adrianna.muciek04@gmail.com

2. **Martyna Mocarska [MM]**

Gabriel Narutowicz Municipal Specialist Hospital, Prądnicka 35 Street, 31-202 Kraków: Cracow, Malopolska, PL

https://orcid.org/0009-0007-4249-9857

e-mail: mocarska99@gmail.com

3. **Anna Orłowska [AO]**

The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow: Cracow, Malopolska, PL

https://orcid.org/0009-0000-6028-3004

e-mail: annaorlosia@gmail.com

4. **Katarzyna Strakowska [KS]**

The Ludwik Rydygier Memorial Specialized Hospital, Osiedle Złotej Jesieni 1, 31-820 Krakow: Cracow, Malopolska, PL

https://orcid.org/0009-0006-6202-2055

e-mail: kasia.strakowska@gmail.com

5. **Laura Opalska [LO]**

The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow: Cracow, Malopolska, PL

https://orcid.org/0009-0007-3122-3484

e-mail: laura.opalska@interia.pl

6. **Anna Maryńczak [AMA]**

Clinical Provincial Hospital No. 2 them. Saint Jadwiga the Queen in Rzeszów, Lwowska 60 Street, 35-301 Rzeszów, Subcarpathia, PL

https://orcid.org/0000-0001-6187-0921

e-mail: annatomon27@gmail.com

7. **Jan Mencel [JM]**

Independent Public Health Care Facility of the Ministry of Internal Affairs and Administration in Krakow, Kronikarza Galla 25 Street, 30-053 Krakow: Cracow, Malopolska, PL

https://orcid.org/0009-0006-0877-2242

e-mail: jan1mencel@gmail.com

8. **Nicole Nitschke [NN]**

The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow: Cracow, Malopolska, PL

https://orcid.org/0009-0003-9817-7903

e-mail: nicolenit99@gmail.com

Abstract

Background: Since antiquity, honey has been recognised for its healing and antibacterial properties. Recently, Manuka honey (MH) has been identified as possessing antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic effects.

Objective: This review examines the potential benefits of manuka honey, its bioactive components, and their effects on cancerogenesis, cancer growth, and development.

Methods: The PubMed and Google Scholar databases were searched, and 46 studies were identified as most relevant to the research objective.

Results: The accompanying papers posit that MH may impede carcinogenesis by regulating various molecular pathways and cancer cell progression. A substantial body of scientific evidence indicates that a range of honey types, including MH, can facilitate the release of reactive oxygen species and cytokines (predominantly IL-1β, IL-6, and TNF-α) by innate immune system cells. Furthermore, studies have demonstrated that honey can stimulate T lymphocytes and macrophages' proliferation and functions while also inducing apoptosis and cell cycle arrest in cancer cells.

Conclusion: The body of evidence attesting to the anticarcinogenic properties of MH continues to grow. Several studies have demonstrated the significant role of manuka honey and its properties in promoting innate and adaptive immunity, which is essential for eliminating cancer cells. Nevertheless, further research is required to provide comprehensive data regarding the active constituents of Manuka honey and their potential efficacy in cancer therapy.

Keywords: Manuka honey, Leptospermum scoparium, anticarcinogenic, cancer

Introduction

The distinctive antimicrobial and anti-inflammatory characteristics of honey have long been recognised, even among ancient civilisations such as those of the ancient Greeks and Egyptians. (McLoone et al., 2016) Honey research aims to identify the bioactive components and distinctive properties underpinning its medicinal applications. In recent years, research has also been conducted into honey's immunoregulatory, antioxidant, anti-inflammatory, antimutagenic and anticarcinogenic effects, in addition to its established high nutritional value and antimicrobial activity. The principal compounds accountable for the antioxidant activity of

honey are flavonoids, phenolic acids, ascorbic acid, catalase, peroxidase, carotenoids and maillards. (Niaz et al., 2017; Margaoan et al., 2021) The composition of these components differs between kinds of honey, depending on the floral origin, geographical location and physiology of the honeybee. (Kavanagh et al., 2019)

MH is produced from the nectar of the Leptospermum scoparium tree, which is indigenous to New Zealand and south-eastern Australia. It is primarily harvested in New Zealand. (Kaźmierczak-Barańska and Karwowski, 2024) Many studies have demonstrated that MH can inhibit the process of carcinogenesis by regulating various molecular processes and the progression of cancer cells. Furthermore, MH can potentially be employed in treating infections caused by multidrug-resistant organisms, which represents a significant advancement in the fight against antimicrobial resistance, given the growing prevalence of multidrug-resistant (MDR) bacteria and their associated public health concerns. (Nolan et al., 2020)

Search methods employed

This study aims to examine the possible effects of MH on cancer and its potential efficacy in treating cancer-related conditions. A comprehensive literature search was conducted using the PubMed and Google Scholar databases, identifying 46 of the most relevant studies to the research objective.

Honey composition

Honey's beneficial properties are influenced by its chemical composition, which varies depending on the type of honey, its floral origin, and the geographical location of the hive (Kavanag, 2018).

Honey contains over 200 macro- and microcomponents, including carbohydrates, water, aromatic compounds, phenolic acids, flavonoids, organic acids, amino acids, proteins, sterols, vitamins, enzymes, essential oils, and pollen particles (Margaoan, 2021). Among the primary carbohydrates present in honey are monosaccharides such as fructose and glucose, disaccharides including sucrose and maltose, and oligosaccharides such as erlose, pentose, maltotriose, nigerose, kojibiose, 3-deoxyglucosulose (3-DG), and methylglyoxal (MGO). The moisture content of honey typically ranges between 10% and 20% of its total weight. Additionally, honey contains various minerals, including aluminium, boron, barium, calcium, chromium, cobalt, copper, iron, potassium, magnesium, manganese, sodium, nickel, phosphorus, sulfur, vanadium, and zinc. Vitamins found in honey include thiamine (B1), riboflavin (B2), ascorbic acid (vitamin C), pantothenic acid, and pyridoxine. Honey is also a source of bioactive compounds such as phenolic acids (e.g., gallic acid, caffeic acid,

chlorogenic acid, benzoic acid, p-hydroxybenzoic acid, 4-hydroxybenzoic acid, 2,3,4-trihydroxybenzoic acid, trans-cinnamic acid, p-coumaric acid, syringic acid, trans-ferulic acid, protocatechualdehyde, protocatechuic acid, and gentisic acid) and flavonoids (e.g., quercetin, luteolin, kaempferol, galangin, isorhamnetin, apigenin, and chrysin). The most frequently identified polyphenolic compounds in honey include gallic acid, syringic acid, quercetin, and luteolin. However, honey may also be subject to contamination by chemical substances, including heavy metals (e.g., arsenic, cadmium, and lead), pesticides, and hydroxymethylfurfural (HMF) (Wang, 2024).

Bioactive properties of honey compounds

The bioactive properties of honey encompass antimicrobial (antibacterial and antifungal), antidiabetic, anti-inflammatory, antioxidant, radical-scavenging, and wound-healing effects (Kavanagh, 2018).

The antioxidant activity of honey arises from its content of flavonoids and phenolic acids, which is supported by ascorbic acid, catalase, peroxidase, carotenoids, and Maillard reaction products.

Manuka honey (MH) is characterised by high concentrations of methylglyoxal (MGO), its primary antibacterial agent. MGO can inactivate bacterial proteins, including those in certain antibiotic-resistant bacteria (e.g., antibiotic-resistant Helicobacter pylori). MGO is a signalling molecule in plant cell cultures that stimulates plant growth. However, elevated intracellular concentrations of MGO can be toxic, leading to protein dysfunction and errors in cellular replication and apoptosis. MGO is also physiologically produced in human cells as a byproduct of anaerobic glycolysis (Wang, 2024; Kazmierczak, 2024).

MH's relatively low pH (approximately 3.5–4.5) further supports microbial growth inhibition. This low pH also contributes to MH's wound-healing properties by reducing protease activity and enhancing fibroblast activity (Margaoan, 2021).

An in vivo study conducted by Kazmierczak and Karwowski (2024) demonstrated MH's radioprotective properties. Fibroblasts treated with MH maintained higher metabolic activity after irradiation than untreated cells (Kazmierczak et al., 2024).

Reports also highlight honey's potential role in regulating blood glucose levels. However, due to its high sugar content, the use of MH for managing diabetes remains controversial (Margaoan, 2021).

In vivo studies of various monofloral honey types have shown that intravenous administration of MH increased the levels of caspase-3 and improved the survival rates of male mice aged 8–12 weeks (Margaoan, 2021).

Cancer Immunology and Manuka Honey Potential Mechanisms of Action

Cancer is defined as a genetic disease induced by multiple mutations affecting genes that regulate the growth and differentiation of cells. (Chan-Zapata and Segura-Campos, 2021) It is currently a widespread condition, representing a leading cause of death in more economically developed countries.

The immune system plays a pivotal role in cancer's pathogenesis, as it can eradicate emerging transformed cells once they arise. This concept is known as 'cancer immunosurveillance'. (Masad et al., 2024) Both innate and adaptive immune system cells recognise tumours and regulate cancer development.

Type of cells	**Mechanism of action**
Innate immune response	
Macrophages	● participation in Th1 pro-inflammatory response ● reactive oxygen (ROS) and nitrogen species (RNS) production ● pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α release
Dendritic cells	● phagocytosis of tumour cells ● presentation of processed antigens to naive T lymphocytes via the major histocompatibility complex (MHC) ● triggering of the immune response of CD8+ or CD4+ T lymphocytes
Neutrophils	● disruption of the plasma membrane of tumor cells opsonized with antibodies ● antibody-dependent trogocytosis
NK cells	● cytolytic activity triggered by the loss of MHC class I molecules on tumour cells ● antibody-dependent cell-mediated cytotoxicity (ADCC)
Adaptive immune response	
Th1 CD4+	● IFN-γ production ● upregulate the mechanisms of antigen processing ● recognition of tumour-associated antigens by CD8+ and CD4+ T cells upregulation ● IL-2 secretion, which mediates the survival, proliferation, and cytotoxic activity of CD8+ T cells
Th2 CD4+	● IL-4, IL-5, IL-10 secretion that allows tumors to evade immune surveillance
Activated CD8+	● detection of tumor-associated antigenic peptides presented by MHC I ● secretion of cytolytic granules (perforins and granzymes) ● IFN-γ and TNF-α secretion
B lymphocytes	● antibodies secretion (initiation of ADCC) ● IFN-γ production

Table 1. Cell types of the innate and adaptive immune system involved in the process of cancer immunosurveillance, based on Chan-Zapata and Segura-Campos, 2021.

Tumour cells are capable of evading the immune system through a number of different mechanisms. These mechanisms encompass defects in MHC class I molecules affecting antigen presentation, reduced cell death signals through altered apoptosis regulation, and immunosuppressive conditions in the tumour environment. The secretion of factors such as IL-10 and TGF-β by regulatory T cells and tumour-associated macrophages can suppress immune responses. Furthermore, tumour-associated macrophages can secrete factors like IL-6 and IL-8, which promote tumour angiogenesis. (Chan-Zapata and Segura-Campos, 2021)

The evidence is mounting to suggest that different types of honey may possess anticancer properties. Some studies have indicated that MH may possess anti-inflammatory properties and modulate anti-tumour immune responses by altering the expression of various cytokines and chemokines. These involve intracellular communication and many physiological and pathological processes, including mediating inflammatory responses. (Navaei-Alipour et al., 2021)

In their study, Aryappalli et al. (2017) identify IL-6R as a direct target of MH, thereby underscoring the potential of IL-6R blockade as a mechanism for the anti-tumour activity of MH and as a viable therapeutic target in IL-6-dependent cancers. Furthermore, the activation of caspases 3/7, 6, 8, and 9 was observed to induce apoptosis in the tumour cells. In vivo studies have also indicated the potential for inhibiting IL-6 production (Keenan et al., 2012; Almasaudi et al., 2016; Almasaudi et al., 2017).

In contrast, several in vitro studies have demonstrated that MH possesses the capacity to stimulate the immune system, resulting in an increase in the production of proinflammatory cytokines by human monocytes, including TNF-α (Tonks et al., 2001), IL-1β and IL-6 (Tonks et al., 2003; Afrin et al., 2018; Gasparrini et al., 2018). The authors posit that these findings indicate that the impact of honey on wound healing may be partially attributable to the stimulation of inflammatory cytokines from monocytic cells. However, they highlight that the mechanisms through which honey influences the release of anti-inflammatory agents and growth factors from monocytic cells remain uncertain, representing a potential avenue for further investigation.

In addition to the impact of MH on cytokine levels, a range of alternative strategies for combating tumour cells were explored. Afrin et al. (2018) described a protective effect on macrophages, whereby the viability of these cells was enhanced, proliferation was promoted, and apoptosis was reduced, with caspase three expression also being decreased. Additionally, Timm et al. (2008) reported the role of facilitating ROS production by monocytes due to the

presence of lipopolysaccharide (LPS), commonly known as endotoxin. Furthermore, MH has been demonstrated to induce the recruitment of neutrophils and the activation of macrophages by inducing the expression of not only proinflammatory cytokines, such as TNF-α and IL-1β but also the chemokines CXCL2 and CCL2, which are potent chemoattractants of myeloid cells (Masad et al., 2022). In their study, Martinetti et al. (2020) demonstrated that MH can influence reactive oxygen species (ROS) and increase intracellular calcium levels, ultimately resulting in cellular death. The mechanism is enhanced by manuka honey's capacity to maintain a high permeability for hydrogen peroxide via the aquaporin 3 (AQP3) channel.

MH was observed to inhibit the proliferation of HCT-116 (human colon adenocarcinoma) cells and their capacity for colony formation accompanied by an induction of ROS production in these cells, as well as apoptosis and cell cycle arrest. (Cianciosi et al., 2020) Moreover, the ability to induce cytotoxicity by inhibiting cell proliferation and viability was observed in two cancer cell lines: human hepatocarcinoma (HepG2) and breast cancer (MCF-7). (Halawani, 2021)

Masad et al. (2024) demonstrated that the administration of MH, whether as a preventive or therapeutic measure, resulted in the enhancement of anti-tumour responses, leading to the suppression or retardation of tumour growth respectively. The enhanced tumour immunogenicity was evidenced by the upregulation of MHC class-II on intratumoral macrophages, the enhanced expression of MHC class-I on tumour cells and the increased infiltration of effector T cells into the tumour microenvironment. Furthermore, there was an observable increase in CXCL10 expression (a chemokine that recruits inflammatory T lymphocytes), a corresponding decrease in CXCL2 expression (which attracts leukocytes) and an elevation of the levels of IFN-γ and granzyme B, both of which are capable of inducing tumour cell apoptosis. Furthermore, the oral administration of MH increased microbiota richness, accompanied by a shift towards more homogeneous and consistent microbiota profiles. Notably, the MH treatment resulted in an enrichment of bacteria with anticancer potential and a reduction in the levels of harmful bacteria, including Staphylococcus and Enterococcus. (Masad et al., 2024)

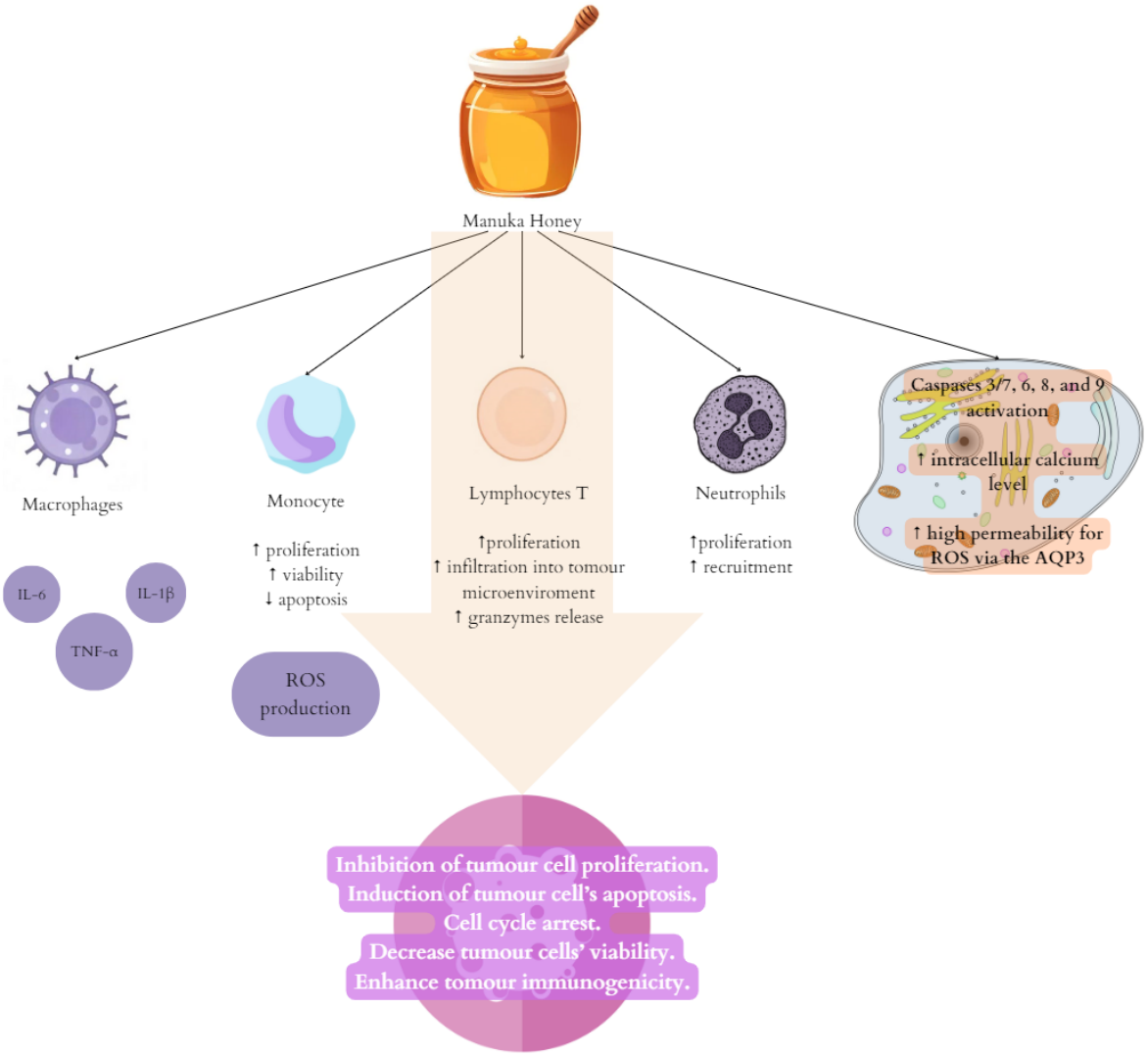

Figure 1. Manuka Honey's mechanisms of action.

Impact of Manuka Honey on Breast Cancer and Lung Cancer

Impact of Manuka Honey on Breast Cancer and Lung Cancer

Ahmed et al. (2017) investigated the effects of two types of honey - Malaysian Tualang honey (TH) and Australian/New Zealand MH - on breast cancer progression in a Sprague-Dawley rat model.

The researchers administered TH and MH to rats that were induced with breast cancer via the carcinogen 1-methyl-1-nitrosourea (MNU). Treatment commenced once the first palpable tumour reached 10-12 mm, and the rats were monitored for 120 days. The study found that both TH and MH significantly inhibited tumour growth. Rats treated with them had smaller tumour sizes, lower weights, and fewer tumours than the untreated positive control group

(Ahmed et al., 2017). Notably, the growth rate of tumours in the honey-treated groups was reduced by up to 70.82%, indicating a substantial antitumor effect.

The study also explored the mechanism behind the antitumor activity of TH and MH, revealing that both kinds of honey modulated tumour growth and apoptosis-related signalling pathways. Administration of TH and MH increased the expression of pro-apoptotic proteins such as Apaf-1, Caspase-9, IFN-γ, IFNGR1 and p53 while decreasing the expression of anti-apoptotic proteins such as TNF-α, COX-2 and Bcl-xL1. This modulation suggests that the anti-tumour effects of TH and MH are mediated through the promotion of cancer cell apoptosis and the inhibition of pathways that typically support tumour survival.

In conclusion, the study by Ahmed et al. (2017) provides compelling evidence that Tualang and MH have potential therapeutic effects against breast cancer, offering a novel, natural adjunct to traditional cancer therapies.

Aryappalli et al. (2017) investigated the anticancer effects of MH on human breast cancer cells (MDA-MB-231 and MCF-7). The study found that MH inhibited the proliferation of these cancer cells in a dose-dependent manner without affecting the non-cancerous MCF-10A cells—MH-induced apoptosis through the activation of caspases and changes in mitochondrial proteins, such as Bax and Bcl-2. A key finding was that MH reduced the phosphorylation of STAT3 (p-STAT3), a crucial oncogenic transcription factor, by inhibiting IL-6 production, which suggests that the IL-6/STAT3 signalling pathway is an early and important target of MH's antitumor effects, positioning it as a potential therapeutic option for breast cancer.

Aryappalli et al. (2019) further explored the mechanism by which MH inhibits p-STAT3 in human breast (MDA-MB-231) and lung (A549) cancer cells. They found that MH selectively binds to the IL-6 receptor (IL-6R) and blocks its interaction with the IL-6 ligand, thereby inhibiting the downstream activation of STAT3. This inhibition was accompanied by a reduction in key signalling components, such as gp130 and phosphorylated JAK2. MH did not affect other cytokine receptors, indicating a specific antagonistic effect on the IL-6R. The study also identified several flavonoids in MH (luteolin, quercetin, galangin, and others) that could bind to IL-6R and block IL-6 binding, further confirming the role of the IL-6/STAT3 pathway in MH's anti-cancerogenic properties of MH.

These findings support the potential of MH as a natural therapeutic agent, particularly for cancers dependent on IL-6/STAT3 signaling, such as breast and lung cancers.

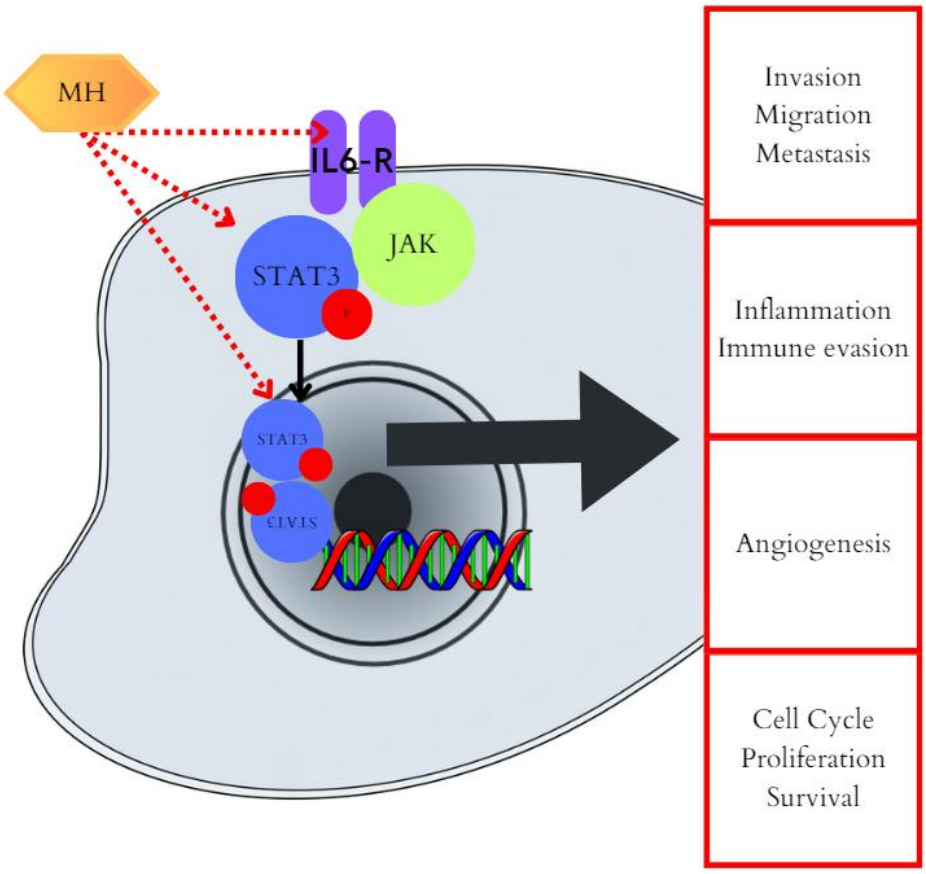

Figure 2. Mechanism of IL-6/STAT3 pathway inhibition by Manuka honey: Manuka honey binds to the IL-6 receptor, blocking the interaction between IL-6 and its receptor, leading to the inhibition of STAT3 activation. This reduces the activation of the signalling pathway associated with cancer cell proliferation and survival—schema based on Aryappalli et al. (2019).

Márquez-Garbán et al. (2020) investigated the antitumor effects of MH in breast cancer models. In vitro, MH inhibited the proliferation of estrogen receptor-positive MCF-7 breast cancer cells in a dose-dependent manner, with minimal effects on non-cancerous mammary epithelial cells. MH induced apoptosis in MCF-7 cells, activating PARP and activating AMPK while inhibiting the AKT/mTOR pathway. Furthermore, the diminished levels of phosphorylated STAT3 were identified following prior research. (Aryappalli et al., 2017, 2019) emphasised the importance of the IL-6/STAT3 pathway in MH's anticancer effects. In vivo, MH significantly reduced MCF-7 tumour growth in nude mice by 84%, supporting its potential as a therapeutic agent in breast cancer.

Impact of Manuka Honey on Prostate Cancer

Abel et al. (2018) made a novel discovery regarding the sugar components of three kinds of honey: New Zealand thyme, manuka, and honeydew. In addition to the phenolics, they have been demonstrated to play a role in the in vitro inhibition of prostate cancer metastatic activity.

The researchers placed PC3 prostate cancer cells in Boyden chambers. They treated them with thyme, manuka, honeydew, or a sugar-only mixture for 48 hours to assess migration and 72 hours to assess invasion. Additionally, the cells were treated with the phenolics quercetin, gallic acid, kaempferol, chrysin, or caffeic acid for the same periods. While the impact of honey on migration was inconclusive, their influence on invasion was markedly evident. This indicates that honey can impede invasion to a greater extent than migration, suggesting that a primary point of inhibition may be more crucial for invasion than migration.

Furthermore, an investigation of PC3 and DU145 prostate cancer cell lines and the three aforementioned honeys in vitro demonstrated a concentration-dependent reduction in cell adhesion to collagen I by 90% ($p < 0.05$), which indicates that honey, in conjunction with the inherent sugars and phenolic components, can impede the metastatic properties of cancer cells. The effect is achieved by hindering the adequate adhesion of cells to the extracellular matrix.

Impact of MH on Colorectal Cancer

Afrin et al. (2017) study showed that MH can induce cell death and increase intracellular reactive oxygen species generation in colon cancer cells. Moreover, it also demonstrated that honey's bioactive compounds depend on its floral sources, geographical origins, and seasonal and environmental factors, significantly impacting its antiproliferative and antioxidant potential.

The Afrin et al. (2018) study investigated the effects of MH on the cytotoxicity and reactive oxygen species (ROS) production induced by 5-fluorouracil (5-FU) in human colon cancer cell lines HCT-116 and LoVo. Combined treatment with 5-FU and MH significantly reduced the IC50 (half maximal inhibitory concentration) values of 5-FU. In HCT-116 cells, the IC50 dropped to 10.43 μM in the presence of 10.5 mg/mL MH. Similarly, in LoVo cells, the IC50 decreased to 20.11 μM with 20.34 mg/mL MH. These findings suggest that MH enhances the cytotoxic efficacy of 5-FU, enabling lower drug concentrations to achieve comparable effects.

When it comes to ROS production, combined treatment with 5-FU and MH further augmented ROS production, increasing levels by 28% in HCT-116 cells and 40% in LoVo cells.

The results indicate that MH synergises with 5-FU to amplify oxidative stress in cancer cells, with greater efficacy observed in LoVo cells.

In conclusion, the data demonstrate that MH markedly enhances the cytotoxic and pro-oxidative effects of 5-FU in colon cancer cells, suggesting its potential as an adjuvant therapy to improve chemotherapeutic outcomes.

Impact of MH on Hepatocellular Carcinoma

A study by Al Refaey et al. (2021) investigated the molecular mechanism and synergistic effect of the anticancer properties of MH on Doxorubicin (DOX)-mediated apoptotic cell death using two different p53 statuses (HepG2 and Hep3B) and a non-tumorigenic immortalised liver cell line. MH treatment exhibited a dose-dependent antiproliferative effect on the cells tested with IC50 concentration of (6.92 ± 0.005%) for HepG2 cells and (18.62 ± 0.07%) for Hep3B cells. It induced radical morphological changes in HepG2 cells characteristic of apoptosis induction after 48 hours of treatment. The results showed that MH or combined treatment were more cytotoxic to p53-wild type, HepG2, cells than to p53-null, Hep3B, cells. Combined treatment of MH and DOX demonstrated a more potent therapeutic effect than the individual treatments, as evidenced by the inhibition of various oncogenic signal transduction proteins, including β-catenin, pERK1/2, mTOR, S6K, and cyclin D1. In normal liver cells, no cytotoxicity was observed.

Impact of MH on Melanoma

In 2013, Fernandez-Cabezudo et al. investigated the impact of MH on the proliferation of cancer cells using murine melanoma (B16.F1), colon carcinoma (CT26), and human breast cancer (MCF-7) cell lines. The viability of B16.F1 melanoma cells was significantly reduced by concentrations of MH ranging from 0.3% to 2.5% in a dose- and time-dependent manner. Following a 24-hour incubation period, the viability of B16.F1 cells decreased to 85%, 75%, 60%, and 43% at MH concentrations of 0.3%, 0.6%, 1.25%, and 2.5%, respectively. The effect was more pronounced following extended incubation periods (48 and 72 hours), with viability reduced to 17% at 2.5% MH after 72 hours. It is noteworthy that the effect of MH was comparable to or exceeded that of taxol, a chemotherapeutic agent, at concentrations of 10 ng/mL and 50 ng/mL.

A dose- and time-dependent increase in apoptotic cells was observed. For instance, at 24 hours, 0.3% MH resulted in 1.5% apoptotic cells compared to 22.3% at 5%. By 72 hours,

apoptosis rates increased significantly, with 35.8% of cells undergoing apoptosis at a 1.25% MH concentration.

These findings confirmed the pronounced inhibitory impact of MH on melanoma cell proliferation, thereby underscoring its potential as a natural antineoplastic agent. MH demonstrates significant anti-melanoma properties through its ability to inhibit proliferation and induce apoptosis in cancer cells. While it shows comparable efficacy to taxol in some contexts, further research is needed to explore its full therapeutic potential and possible synergistic effects with existing chemotherapeutics.

Impact of MH on Squamous Cell Carcinoma

In 2015, Drain and Fleming published a case study in which they described the use of MH by a female patient with advanced oral cavity squamous cell carcinoma.

The patient presented with an inflamed, painful, open wound to the lower face with a protruding bone fragment and purulent drainage measuring 2 cm x 2 cm. Additionally, multiple tumours had ulcerations inside the mouth along the mandible. She experienced difficulties managing the wound and the malodor that originated in the oral cavity. In order to alleviate the symptoms, two forms of MH were employed. Calcium alginate with MH was applied to the external wound, while MH paste was used on the oral wounds. Following one week, the wound had improved, with reduced inflammation, decreased drainage, and no malodor. After three months, the external wound had decreased in size to 1 cm x 1 cm, with no signs of inflammation and no odour. A low volume of serosanguineous drainage was observed. The patient reported the wound to remain tender and painful to the touch but that the discomfort was less severe than it was prior to undergoing treatment.

Effects of Manuka Honey in conjunction with anticancer therapy

- **Oral care for radiation-induced oral mucositis**

Regrettably, the beneficial effects of MH in reducing the severity of radiation-induced mucositis in head and neck cancer patients have not been substantiated. In a double-blind, randomised, placebo-controlled trial conducted by Hawley et al. (2014) involving 106 patients from the Vancouver and Sudbury Cancer Centres in Canada, no statistically significant difference was observed between the honey and placebo groups despite the administration of 5ml of MH daily during radiation and for 7 days post-radiation. Notwithstanding the aforementioned result, a high drop-out rate was observed. Approximately 57% of the honey

and 52% of the placebo groups did not complete this study, which can be attributed primarily to the nausea induced by the side effects of therapy, both chemotherapy and radiation, administered simultaneously. Furthermore, the taste and smell of the MH exacerbated the nausea. (Hawley et al., 2014)

A further double-blind, placebo-controlled, randomised trial conducted by Bardy et al. (2012) reported no significant improvement in oral mucositis outcomes. Additionally, the study examined the impact of MH on the oral microbiome. In the trial, 67 participants were allocated to the MH group, while 64 participants in the control group received golden syrup. The findings indicated no statistically significant differences in oral pathological colonisation between the two groups. Moreover, MH did not demonstrate any discernible benefits in reducing tube feeding dependency or preventing weight loss throughout the study. (Bardy et al., 2012)

In their systematic review, "Natural Agents in the Management of Oral Mucositis Caused by Radiation of Head and Neck Cancer", Nagi et al. identified comparable outcomes regarding the use of MH. They concluded that the benefits of MH are questionable due to its poor patient tolerance. Many individuals experienced nausea and vomiting, which limited its practical use. These adverse effects significantly impacted patient compliance, reducing the treatment's potential effectiveness in clinical settings. (Nagi et al., 2018)

In contrast, four other trials conducted by Motallebnejad et al. (2008), Khanal et al. (2010), and Bardy et al. (2012) examined the use of alternative types of honey rather than MH. The aforementioned studies have indicated a notable reduction in ulceration and lesions associated with oral mucositis, suggesting that alternative honey varieties may offer enhanced benefits with fewer tolerability issues. These findings highlight the necessity for further research to identify the most efficacious and patient-friendly natural agents for managing oral mucositis.

- **Chemoradiation Therapy-Induced Esophagitis**

In 2016, Fogh et al. conducted a study to evaluate the efficacy of MH in reducing or delaying pain associated with oesophagitis during chemoradiation treatment in lung cancer patients. Prior to the trial, patients were stratified according to the oesophagus receiving 60 Gy (V60Gy oesophagus $<$ or $\geq$ 30%) and then randomised to receive either daily standard supportive care, 40 ml of liquid MH or 8 MH lozenges during chemoradiation treatment (Fogh et at., 2016). Patients were required to report the pain associated with oesophagitis using the Numerical Rating Pain Scale (NRPS) and to track the severity of dysphagia throughout their treatment. Furthermore, data about patients' weight, nutritional status and opioid use were also

collected. The data were collected at the baseline and 4 and 12 weeks. At four weeks, no significant difference was observed between the groups: supportive care vs. liquid honey ($p = 0.92$) or supportive care vs. lozenge honey ($p = 0.93$). At the 12-week mark, there was a notable improvement in the NRPS between the supportive care and lozenge MH groups ($p=0.02$), with the lozenge arm showing a more favourable outcome. The only other statistically significant difference was observed in the opioid use at the 4-week interval ($p=0.03$), with more patients in the supportive care group requiring their use. (Fogh et al., 2016)

- **Disorders of the Skin**

In vitro studies, including those by Kronda et al. (2013), demonstrate that honey varieties such as Manuka and Medihoney can effectively combat wound pathogens like MRSA and Pseudomonas aeruginosa, disrupt biofilms, and reduce microbial virulence. Notably, as highlighted in McLoone et al.'s systematic review (2016), MH can reverse antimicrobial resistance by synergising with oxacillin to inhibit MRSA and restore its antibiotic susceptibility. Honey also shows efficacy against microbes linked to skin conditions like S. aureus, Candida albicans, dermatophytes, and Propionibacterium acnes, associated with impetigo, acne, and tinea infections (Kronda et al., 2013; McLoone et al., 2016). Honey's immune-modulating properties and potential to promote re-epithelialisation, angiogenesis, and cell proliferation by enhancing cell adhesion and migration have also been observed, essential for early healing and aiding chronic wound repair.

Specific other findings include:

- Rosacea: Kanuka honey showed promising results in the study by Braithwaite et al. (2015), outperforming control creams in reducing severity.
- Acne: According to Semprini et al. (2016), honey combined with antibacterial soap provided no additional benefits compared to soap alone.
- Eczema and Psoriasis: Medical-grade Kanuka honey was as effective as standard creams but less effective than corticosteroids (Fingleton et al., 2014).
- Cold Sores:Honey achieved healing times comparable to Acyclovir but with limited sample sizes (Fingleton et al., 2014).

While in vivo evidence supports honey's wound-healing properties, as noted in the Cochrane review by Jull et al. (2015), inconsistencies in study quality emphasise the need for more extensive, well-designed clinical trials.

Discussion

Cancer is a genetic disease that represents an increasing global public health concern. Dietary therapy's potential in preventing and treating this condition represents a promising avenue for its management. Manuka honey, renowned for its unique antibacterial qualities, has attracted considerable attention in recent years concerning its potential anticarcinogenic properties. Derived from the nectar of the Leptospermum scoparium plant in New Zealand, this honey variety contains distinctive bioactive compounds that may contribute to the prevention and treatment of cancer.

A literature review reveals that MH's distinctive chemical composition, including methylglyoxal (MGO), flavonoids, and phenolic acids, is associated with its potential anticancer effects. These compounds act in concert to disrupt cancer cell metabolism, enhance immune response, and protect normal cells from oxidative stress. Furthermore, the distinctive peroxide activity in manuka honey may intensify the damage caused to cancer cells when combined with its exceptional capacity to keep AQP-3 channels open, thereby increasing oxygenic stress in these cells. All of these mechanisms make honey an encouraging natural agent for use in cancer therapy. (Martinetti et al., 2020)

MH has been shown to inhibit the proliferation of various cancer cell lines, including breast, colon, and prostate cancers. By interfering with DNA synthesis and inducing cell cycle arrest, manuka honey effectively slows down or halts the multiplication of cancer cells. Furthermore, MH has been demonstrated to enhance apoptosis, or programmed cell death, which represents a natural mechanism the body employs to eliminate damaged or unwanted cells. This process has been observed in cancer cells, where MH has been shown to upregulate pro-apoptotic genes and downregulate anti-apoptotic genes.

MH exerts a multifaceted influence on the immune system. As chronic inflammation is an established risk factor for cancer development and progression, the anti-inflammatory properties of Manuka honey assist in mitigating this risk by reducing inflammatory cytokines and modulating immune responses. This prevents the initial stages of carcinogenesis and facilitates the management of tumour growth and metastasis.

The antioxidant activity of manuka honey is vital in protecting cells from oxidative damage caused by free radicals. By neutralising these harmful molecules, manuka honey plays a role in maintaining genomic stability and preventing mutations that can lead to cancer. Furthermore, antioxidants bolster the body's intrinsic defensive capabilities, thus enhancing overall health and resilience against the development of cancerous cells.

The anticarcinogenic properties of manuka honey are the subject of ongoing clinical trials and laboratory studies. Ongoing research is focused on identifying and optimising the specific compounds responsible for these effects, which could lead to the development of novel therapeutic applications. Additionally, the research compares the in vivo and in vitro activity of MH, examines the differences between various administration methods, and investigates the impact of varying doses of MH on biological processes. Such studies will likely identify a method of utilising MH's distinctive anticarcinogenic characteristics in the practical treatment of neoplasms. For example, Idriss et al. (2024) conducted a comparative analysis of the constituents and antiproliferative effects of raw and powdered MH (pMH) on human and murine cancer cell lines. The human cell lines included MDA-MB-231 breast cancer cells and A549 lung cancer cells, while the murine cell lines were B16.F10 melanoma, CT26, and MC38 colorectal adenocarcinoma cells. Notable discrepancies were observed in the bioactive constituents present in the raw and pMH samples, including flavonoids, phenols, terpenoids, carbohydrates, and organic acids.

Furthermore, several altered metabolic pathways were identified in pMH compared to raw MH, encompassing energy metabolism, amino acid metabolism, xenobiotic biodegradation, and a range of other regulatory pathways. Nevertheless, the raw and powdered MH samples exhibited a dose-dependent inhibitory effect on tumour cell growth. The authors posit that the observed pathway alterations may influence cancer cell behaviour, underscoring their role in regulating cancer growth.

Moreover, a comparative analysis was conducted by Cianciosi et al. (2020) to assess the inhibitory effects of MH and DMH (digested MH) on the proliferation of HCT-116 (human colon adenocarcinoma) cells, the induction of ROS production in these cells, the induction of apoptosis, cell cycle arrest, and colony formation ability. Despite a change in the content of phenolic compounds, the antioxidant capacity decreased to a much lesser extent due to the presence of other bioactive compounds. The study demonstrated that MH and DMH exhibited similar effects in the induction of intracellular ROS production and the inhibition of colony formation in HCT-116 cell lines. It was also observed that there was a notable difference in the timing of the cell cycle arrest between MH and DMH, with progression halted in the S phase by MH and in the Sub-G1 phase by DMH.

Prior research has indicated that manuka honey exhibits immunostimulatory properties influencing both the innate and adaptive systems, particularly macrophages and the production of cytokines such as IL-1β, IL-6, and TNF-α, as well as ROS. These properties play a pivotal role in the immunological processes that facilitate the elimination of cancer cells. Furthermore,

MH's ability to inhibit cell proliferation, induce apoptosis, reduce inflammation, and protect against oxidative stress underscores its potential as a valuable natural adjunct in oncological therapies. Nevertheless, further research is necessary before honey and its constituents can be considered a potential therapeutic agent. Manuka honey may become integral to comprehensive cancer care strategies as research progresses.

Authors' contributions statement

Conceptualization: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Data Curation: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Formal Analysis: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Funding Acquisition: Investigation: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Methodology: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Project Administration: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Resources: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Software: [AM] [MM] [AO] [KS] [LO] [AMA][JM][NN]
Supervision: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Validation: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Visualization: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Writing- original Draft: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
Writing- Review and Editing: [AM] [MM] [AO] [KS] [LO] [AMA][NN]
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