

REVIEW ARTICLE



## Bee honey and cancer

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### Summary

The benefits of bee honey in human health have long been recognized. Honey possesses antioxidant, chemopreventive, anti-atherogenic, immunoregulatory, antimicrobial and wound healing properties, however, the effects of honey on immune functions and its antitumour activity are not well characterised. This review explores the immunomodulatory and antitumour activity of bee honey in experimental studies and clinical studies and provides a broader perspective on the use of honey in the cancer setting. Evidence to support the use of honey in the treatment of radiation-induced mucositis, radiotherapy-induced and chemotherapy-induced skin reactions, the oral cavity and external surgical wounds is presented.

**Keywords:** Honey, cancer, immunomodulation, wound care, radiotherapy, chemotherapy

### Introduction

Malignant diseases are responsible for the death of about one fifth of the population. There is no curable treatment for the majority of malignancies, while all therapeutic regimes produce varying side effects, including haematological toxicity. The administration of different chemotherapeutic agents (even with those of natural origin, such as epirubicin, taxol, and irinotecan) has been suggested to result in early bone marrow depression (Oršolić and Bašić, 2005; Oršolić *et al.* 2008a). Moreover, extensive radiotherapy which covers wide parts of the bone marrow can lead to the development of a complex, dose dependent series of haematopoietic syndrome. Enhanced susceptibility to infections with opportunistic microorganisms occurs in parallel with progressive radiation-induced atrophy of lymph nodes, spleen, and bone marrow (Oršolić *et al.* 2007; 2008a). It has been suggested that radioprotective activity conferred by immunomodulators can be attributed to their capacity to enhance haematopoietic and immune functions.

Also, 20–40% of all cancer patients receiving intensive chemotherapy suffer from mucositis; the number increases to 80% when chemotherapy and radiation are combined, and is higher in patients receiving treatment for cancer in the head and neck (Simon

*et al.* 2009). Open sores in cancer patients suffering from mucositis leave them susceptible to infection.

There are an increasing number of reports of natural products that inhibit tumour cell growth and metastasis, as well as those that induce apoptosis. These bring hope of improved treatment for human tumours (Oršolić and Bašić, 2007; Oršolić *et al.* 2008a and b). Various signalling pathways, including stimulation of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) release, inhibition of cell proliferation, induction of apoptosis and cell cycle arrest, as well as inhibition of lipoprotein oxidation, mediate the beneficial effects exerted by honey and its major components such as chrysin and other flavonoids (Tonks *et al.*, 2001; Swellam *et al.*, 2003; Mabrouk *et al.*, 2002; Gheldof *et al.*, 2002; Woo *et al.*, 2004).

The benefits of bee honey in human health have long been recognized. Athenaeus, the Greek philosopher and author of "*The deipnosophists*", reported that Democritus (500 BC) used honey in his daily diet for longevity and fertility. Democritus, Hippocrates and Discorides all considered honey as an important agent for the strengthening of the body and the promotion of health. Plato's concepts of a healthy diet consisted of cereals, legumes, fruits, milk, honey and fish (Skiadas and Lascaratos, 2001).

### **The investigation of the anti-cancer effects of honey using tumour cell lines *in vitro***

In recent years, considerable efforts have been made to identify naturally occurring and related synthetic agents that could prevent the development and recurrence of cancer. Cancer chemoprevention therefore has emerged as an important subject that, in addition to providing a practical approach to identifying potentially useful novel agents as inhibitors of cancer development, offers opportunities to study the mechanism of carcinogenesis.

The anti-proliferative effect of honey in bladder cancer cells was reported using T24, RT4, 253J and MBT2 bladder cancer cell lines *in vitro* (Swellam *et al.*, 2003). Significant inhibition of the proliferation of T24 and MBT-2 cell lines by 1–25% honey and of RT4 and 253J cell lines by 6–25% honey was observed. Cells treated with 3% honey showed significant cell arrest in the sub-G1 phase after 24 h that was at comparable levels to the arrest induced in C6 glioma cells by caffeic acid phenyl esters (CAPE) (Lee *et al.*, 2003). According to Swellam and colleagues, the effect of honey on cell growth depends on the cell line and concentration of honey; Moreover, honey induced apoptosis was associated with the activation of caspase-3 by CAPE (Lee *et al.*, 2003). Induction of apoptosis by honey has also been reported in colon cells. Results by Jaganathan and Mandal (2009 a and b) indicate that honey exerted a significant anti-proliferative effect on two colon cancer cell lines (HCT 15 and HT 29). Here the MTT assay revealed that the honey sample which containing a high phenolic content showed a significant anti-proliferative effect, and again the growth inhibition response varied with the cell line and concentration used.

Oestrogen agonists or antagonists function in a cell and tissue-type specific manner. Honeys from various floral sources have been shown to be rich in phenolic compounds, which are substances known to mediate oestrogen effects via modulation of oestrogen receptor activity (Merken and Beecher, 2000; Gomez-Caravaca *et al.*, 2006; Moutsatsou, 2007). Tsiapara *et al.*, (2009) investigated the influence of Greek honey extracts (thyme, pine and fir honey) on the oestrogenic activity and cell viability of breast (MCF-7), endometrial (Ishikawa) and prostate (PC-3) cancer cells. Thyme honey reduced the viability of Ishikawa and PC-3 cells, whereas fir honey stimulated the viability of MCF-7 cells. The authors concluded that modulation of oestrogen activity was linked to the rich phenolic content of Greek honeys and suggested that a thyme honey-enriched diet may prevent cancer related processes in breast, prostate and endometrial cancer cells. Polyphenols and phenolic acids (such as vanillic acid, protocatechuic acid and p-hydroxybenzoic acid) have been reported to inhibit cancer-related pathways and processes (Kris-Etherton *et al.*, 2002; Yech, *et al.*, 2005; Yech and Yen, 2005), including prostate cancer (Chan *et al.*, 2005; Von Low *et al.*, 2007) and endometrial cancer (Burton and Wells, 2002). Recent data (Michail *et al.*, 2007) indicated that the

abundance of hydroxymethylfurfural in thyme honey might have antitumour potential.

### **The investigation of the anti-cancer effects of honey using animal models:**

Some animal studies indicate that honey possesses moderate antitumour and pronounced antimetastatic effects (Gribel and Pashinskii, 1990; Swellam *et al.*, 2003; Al-Waili, 2003a). Furthermore, honey has been shown to potentiate the antitumour activity of chemotherapeutic drugs such as 5-fluorouracil and cyclophosphamide (Gribel and Pashinskii, 1990). Honey contains many biologically active compounds including caffeic acid, caffeic acid phenethyl ester and flavonoid glycones. These compounds have been demonstrated to have an inhibitory effect on tumour cell proliferation and transformation by the down regulation of many cellular pathways via proteins such as tyrosine kinase, cyclooxygenase and ornithine decarboxylase (Oršolić and Bašić, 2007).

In an experimental study the effect of honey on metastasing ability in murine and rats tumour models was investigated (Oršolić *et al.*, 2003; 2005). Two transplantable murine tumours (a mammary carcinoma [MCA] and a methylcholanthrene-induced fibrosarcoma [FS] of CBA mouse) and an anaplastic colon adenocarcinoma [ACA] of Y59 rat, were used respectively. Metastases in the lung were generated by injecting viable tumour cells intravenously. It was shown that treatment with honey exerted a pronounced antimetastatic effect in both types of murine tumour ( $p < 0.01$  and  $p < 0.001$ , respectively) when given orally (2 g / kg) once a day for 10 consecutive days before tumour cell inoculation (Oršolić *et al.*, 2003; 2005). Honey given 2 days after tumour cell inoculation had no effect or even increased the number of tumour nodules in the lung. Curative treatment of mice did not affect the weight of lungs indicating that a possible development of micrometastatic foci in lungs did not influence the weight of lungs up to day 21 after tumour cell inoculation. In the rat model, honey given orally (1 g / kg) significantly ( $p < 0.01$ ) affected the formation of lung metastasis when applied before tumour cell inoculation; however when given to rats after tumour cell inoculation, honey enhanced metastasis formation in the lung. The latter suggests that the antitumour effect of honey mostly depends on the time of application; it is likely that polyphenolic components present in honey stimulate host antitumour defences, yet in the presence of a tumour, the nutritive constituents of honey prevail. It is possible that honey promotes tumour growth since it contains a mixture of vitamins, minerals and amino acids, as well as large amounts of glucose. In addition, its high osmolarity induces an outflow of lymph which enhances nutrition and oxygenation, and its acidity favours release of oxygen from haemoglobin in the capillaries of adjacent tissues.

Honey in combination with chemotherapeutics (5-FU or adriamycin) may prevent chemotherapeutic-induced toxicity on

leukocyte populations in peripheral blood (Oršolić and Bašić 2004a, b). Additionally, the preventive treatment of mice with honey significantly increased the activity of macrophages, as compared to a control group of mice. These results, in line with other reports (Caltagirone *et al.*, 2000; Suzuki *et al.*, 2002; Al-Waili, 2003 a; Oršolić *et al.*, 2003; Oršolić and Bašić 2004a,b; Conclin, 2004; Oršolić *et al.*, 2005) suggest that flavonoids from honey possess haemostimulative, antioxidative, protective and regenerative properties. Flavonoids possess the ability to capture and deactivate free radicals (Caltagirone *et al.*, 2000; Suzuki *et al.*, 2002; Chen *et al.*, 2004) thereby inhibiting the binding of free radicals to DNA, allowing activation of the detoxication system and protection of capillary partitions (Caltagirone *et al.*, 2000; Suzuki *et al.*, 2002; Chen *et al.*, 2004). The unique structure of flavonoids in trapping free radicals and their neutralization by two hydrogen atoms, is achieved by two thiols (Chen *et al.*, 2004). Al-Waili (2003 a) showed that honey increased the amount and activity of antioxidant agents such as vitamin C by 47%, beta-carotene by 3%, uric acid by 12% and glutathione reductase by 7%. These compounds reduce the extent of lipid peroxidation, which is a consequence of toxic metabolites generated by the biotransformation of chemotherapeutic agents (Al-Waili, 2003 a; Oršolić *et al.*, 2005). It is possible that the antioxidant capacity of honey is a result of the combined activity of a wide range of compounds including phenolics, peptides, organic acids, enzymes, Maillard reaction products, and possibly other minor components and that the phenolic compounds contribute significantly to the antioxidant capacity of honey but are not solely responsible for it.

Bee honey is an effective agent when administered intravesically or orally in the MBT-2 bladder cancer implantation model; intravesical injection of 6 and 12% honey, as well as oral ingestion of honey significantly inhibited tumour growth (Swellam *et al.* 2003). The mechanism of the antitumour effect shown in this study is unclear, but it may be related to the inhibitory effect of caffeic acid esters and flavonoid glycones on tyrosine protein kinase, lipoxygenase, and cyclooxygenase pathways metabolites. Thus, caffeic acid (3,4-dihydroxycinnamic acid) ester derivatives which are present in honey at levels of 20–25%, are thought to exhibit a broad spectrum of activities that possibly include tumour inhibition.

Another possibility may be the effect of honey as a probiotic agent because it contains 4 to 5% fructooligosaccharides. Numerous studies have confirmed the stimulating effect of honey on colonic probiotic bacteria (Shamala *et al.*, 2000; Chow, 2002; Ezz El-Arab *et al.*, 2006). Oral administration of *Lactobacillus casei* has been demonstrated to suppress tumour growth and thus prolonging survival in animals with experimental bladder tumours and preventing recurrence in a post-resection tumour recurrence model (Karasawa 1987). Several studies show that colonic probiotic bacteria can remove mycotoxins (a natural carcinogen) via physical

binding (Gratz *et al.*, 2004; Ezz El-Arab *et al.*, 2006). In addition, the severity of mycotoxin poisoning can be amplified by factors such as vitamin deficiency, caloric deprivation, alcohol abuse and infectious disease status (Bennett and Klich, 2003).

Hamzaoglu *et al.* (2000) demonstrated that the application of commercial honey to surgical wounds in mice impeded subsequent tumour implantation. Dr. Hamzaoglu's group evaluated tumour implantation (TI) in 60 mice by inoculating surgically created neck wounds with transplantable Ehrlich ascites tumour. In half of the mice, the investigators coated the surgical wound with honey before and after tumour inoculation. The remaining mice served as controls. Tumour implantation was successful in all control mice while in honey-treated mice, no tumours were found on gross examination, but histological analysis revealed implantation in eight cases. Despite this finding, tumour implantation still occurred significantly less often in honey-treated mice than controls ( $p < 0.001$ ). It seems to be that honey may act as an effective barrier and it may also inhibit proteolysis of the basal membrane that occurs during tumour cell invasion. Liotta (1984) proposed a 3-step hypothesis describing the sequence of biochemical events during tumour cell invasion of the extracellular matrix: attachment of the tumour cell, local proteolysis of the basal membrane, and locomotion of the tumour cells within the tissue. The results of this study suggest that honey provides a simple, effective, and harmless barrier to TI by eliminating tumour cell attachment, although honey might inhibit the local proteolysis step. The hypertonicity of honey itself may also create a destructive environment around the tumour cells that ultimately causes cell shrinking. The authors concluded that honey may also provide benefit in conventional oncological surgery where tumour implantation is predictable (Hamzaoglu *et al.* 2000). In laparoscopic surgery, honey could be used on trocar wounds of patients with malignant disease to prevent trocar site recurrence.

Ayyıldız *et al.* (2007) evaluated the histopathological effects of intraurethral applied honey on urethral wound healing and forming scar tissue after urethral injury in a rat model. This experimental model is important for the surgical procedure of urinary bladder cancer in human. Wound healing after an injury is a process which begins with inflammation and ends with the formation of scar tissue. This process is a complex event which includes extracellular matrix, cells, growth factors and cytokines (Da Silva *et al.*, 2002, Kumar *et al.*, 2009). The most important factors for the formation of scar tissue are the aggregation and proliferation of fibroblasts in the wound site and the increases in the accumulation of other extracellular matrix components such as collagen and glycosaminoglycans (GAG) (Da Silva *et al.*, 2002, Kumar *et al.*, 2009). The extracellular matrix plays an important role in the biophysical properties of the tissue during the healing process of urethral injury and leads many prognostic events. The most important problem which occurs after urethral injury is the decrease of urine flow, which

arises as a result of scar development and urethral stricture. Intraurethral application of 10% honey during 1 week or 3 weeks prevented inflammation and accelerated urethral healing. The application of honey after urethral injuries was thought to prevent the development of urethral strictures and scar formations.

Fukuda *et al.* (2009) demonstrated that Jungle honey (collected from tree blossom by wild honeybees that live in the tropical forest of Nigeria) enhanced immune functions and antitumour activity in mice. C57BL/6 mice were injected intraperitoneally with Jungle honey (JH) at dose of 1 mg/mouse/day during seven days and antitumour activity was assessed by growth of Lewis Lung Carcinoma/2 (LL/2) cells. Tumour incidence and weight were decreased in JH-injected mice while the number of peritoneal cells (PC) and migration of neutrophils was increased as well as the production of reactive oxygen species (ROS) in PC cells. ROS produced by activated neutrophils has tumour cytotoxic properties in addition to preventive action against infection. JH-induced neutrophils in the peritoneal cavity were activated by IL-1, which was produced by JH stimulation. Since infiltration of many neutrophils was observed at necrotic areas in JH injected-tumour tissue, there is a possibility that antitumour activity by JH is due to the production of ROS by infiltrated neutrophils into tumour tissue.

## Clinical studies with cancer patients

### Effectiveness of honey in the treatment wounds of urogenital carcinomas

The first reported use of honey in oncology patients was the topical application of 'household' honey to 12 patients with wound breakdown following radical excision of vulval carcinoma. Clearance of infection was observed within 3-6 days, and improved healing rates were recorded (Cavanagh *et al.*, 1970). In a report from the Russian Academy of Medical Science, patients with uterine cancer undergoing radiotherapy and treated with 'honey laminolact' showed a significant decrease in the severity of radiation-induced intestinal morbidity (Smirnova, 2000).

### Honey treatment for prevention of oral mucositis

Many cancer patients suffer from mucositis, a side effect of chemotherapy that attacks the entire gastrointestinal tract from the mouth to the anus. Mucositis is a result of imbalance between cell loss and cell proliferation. The cancer treatment breaks down the epithelial cells lining the tract, leaving the patient prone to ulcerations and infections. These important cells normally replicate and divide rapidly, which is why in a typical healthy individual wounds in the mouth heal quickly. Chemotherapy does not distinguish between healthy and malignant cells, attacking all that reproduce rapidly, including these epithelial cells.

According to the World Health Report cancer accounted for 7.1 million deaths in 2003, and it is estimated the overall number of new cases will rise by 50% in the next 20 years (World Health Organization & International Union against Cancer, 2003). Oropharyngeal cancer is more common in developing countries (Stewart *et al.* 2003, Petersen, 2003). Radiotherapy plays an important role in the management of head and neck cancer. The majority of new cases with invasive head and neck cancer will require radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as a palliative therapy. Most patients with head and neck carcinomas, treated with curative intent, receive a dose between 50 and 70 Gy. This dose is usually given in 2 Gy fractions once a day for five days a week over a five to seven week period (Motalebnejad *et al.*, 2008). In addition to an anti-tumour effect, ionizing radiation causes damage to normal tissues located in the radiation portals. In head and neck cancer patients, radiotherapy has been shown to affect not only skin, but also mucosa, subcutaneous tissues, bone, and salivary glands. The most common acute complication of radiotherapy in the head and neck region is oral mucositis. Radiation mucositis is considered to be an inevitable but transient side effect of therapeutic head and neck irradiation and is strongly related to radiation dose, fraction size, volume of irradiated tissue, fractionation scheme, and the type of ionizing irradiation.

The clinical value of honey and its role in cancer was recently reviewed (Bardy *et al.*, 2008). In the cancer setting, honey has been found to be effective in radiation-induced oral mucositis, stomatitis, periodontal gum disease, radiotherapy-induced skin reactions, hand and foot skin reactions in chemotherapy patients and for oral cavity and external surgical wounds, malignant ulcers and infected lesions in paediatric oncology patients (Chiba *et al.*, 1985; Smirnova *et al.*, 2000; Biswal *et al.*, 2003; English *et al.*, 2004; Moolenaar *et al.*, 2006; Simon *et al.*, 2006).

Results of two preliminary studies suggest that honey may protect oral mucosa from radiation damage (Biswal *et al.*, 2003; Motalebnejad *et al.*, 2008). Biswal *et al.* (2003) investigated the use of honey in 40 adult patients with head and neck cancer. In the study, patients were advised to take 20 ml of pure honey from the tea plant (*Camellia sinensis*) 15 min before, 15 min after and 6 h post -radiation therapy. There was a significant reduction in the symptomatic grade 3/4 mucositis among honey-treated patients compared to controls; i.e., 20% versus 75% ( $p < 0.001$ ). Fifty-five percent of patients treated with topical honey showed no change or a positive gain in body weight compared to 25% in the control arm ( $p = 0.053$ ); the majority lost weight. However, there was no significant change in grade 1 and 2 mucositis. The authors concluded that topical application of natural honey to be a simple and cost-effective treatment in radiation mucositis, which warrants further investigation in a multi-centre randomized trial (Biswal *et al.*, 2003).

In Iran, a similar study and a significant reduction in mucositis among honey receiving patients compared with controls ( $p=0.000$ ) was demonstrated by (Motalebnejad *et al.*, 2008). In a randomized single blind clinical trial with 40 patients twenty patients assigned to the study group received honey and astragale (20 ml of honey 15 minutes before radiation therapy, then again at intervals of 15 minutes and six hours after radiation), while both the study and control groups received standard head and neck radiation therapy based on a standard protocol. Control group patients used 20 ml of saline before and after radiation. The authors suggest that honey was a pleasant, simple and economic modality for the management of radiation mucositis (Motalebnejad *et al.*, 2008).

Robson and Cooper (2009) suggested *Leptospermum* honey to manage wounds/skin impaired by radiotherapy. In four patients where the use of conventional dressings did not facilitate healing, wound healing was facilitated by honey. Compromised areas involved the neck, cheek, groin/perineum, and chest. In two patients, after topical application of honey via hydrofiber rope and nonadhesive foam, respectively, improvements in the size and condition of wound/per wound area and a reduction in pain were noted before death or loss to follow-up. After including honey in the treatment regimen of other two patients, complete healing was noted in 2.5 weeks (with honey and paraffin) and 6 weeks (with honey-soaked hydrofiber rope), respectively. No adverse events were reported. It was concluded that honey might be used as an adjunct to conventional wound/skin care and that prospective, randomized controlled clinical studies with larger numbers of patients are needed to establish the healing potential of honey and to determine optimum treatment protocols (Robson and Cooper, 2009).

Mucositis may lead to sub-optimum effectiveness of chemotherapy and radiotherapy and bacterial colonisation of the oral mucosa can aggravate pre-existing mucositis (Al-Tikriti *et al.* 1984). Endotoxins released by Gram negative bacilli are potent mediators of an inflammatory process (Bernhoft and Skaug, 1985). Honey was also found to reduce microbes within the oral cavity in head and neck cancer patients (Sela *et al.*, 2000). This suggests that there is further scope for the use of honey within the cancer setting and particularly in the care of wounds in head and neck cancer patients.

#### **Effectiveness of honey in treatment wounds of breast and other cancers**

In a prospective, controlled randomized study (Moolenaar *et al.*, 2006) involving 24 skin reactions in 21 breast cancer patients with grade 3 skin toxicities (RTOG Criteria) larger than 15 mm in diameter, honey gauze (HoneySoft®) demonstrated a trend toward faster healing and reduced discomfort in radiation-induced skin toxicity when compared to paraffin gauze (Unitulle®), but the study sample size was insufficient for statistical analysis.

Dunford (2001) described the treatment of a patient with mantle cell lymphoma who acquired a severe wound infection and abdominal cellulitis following a lymph node biopsy from the right thigh. Treatment included larvae therapy (LarvE), vacuum-assisted closure (VAC), and *Leptospermum* honey. Applied chemotherapy, together with the patient's state, resulted in severe infection and the disruption of the immune system of patient. Honey applied to the wound, which was approximately 12 cm in length and extended down to the peritoneum, showed continued healing, with no adverse events until the wound was completely healed and free of MRSA, *Staphylococcus aureus* and *Enterococcus spp.* within 4 weeks of starting the honey treatment. Specified honey therapy was not only able to debride and assist in the eradication of the infection, but was also able to help generate new tissue needed for full closure in a relatively short period (14 weeks).

Simon *et al.* (2009) showed the effect of Medihoney™ on one patient with acute myeloid leukaemia in relapse. The patient had a wound infection with methicillin-resistant coagulase-negative *Staphylococcus* after thoracic surgery for invasive *Aspergillus* infection of the lung, but was allocated to allogeneic bone marrow transplantation. Using medical honey, the infection was eliminated. The patient continued to receive medical honey applications during and after the transplantation, leading to a successful healing without further local or systemic complications.

#### **The use of medical honey to treat diverse wounds in paediatric oncology patients**

In paediatric oncology patients, the immune system is often suppressed by cytotoxic antineoplastic agents or radiation therapy and wound healing is impaired. In the Department of Paediatric Oncology at the Children's Hospital in the University of Bonn, Medihoney™ has become a readily accepted treatment with a positive impact on patient and parent satisfaction (Simon *et al.*, 2006; Sofka *et al.*, 2004; Blaser *et al.*, 2007). The eradication of MRSA from diverse wounds in pediatric oncology patients has also been reported (Sofka *et al.*, 2004; Blaser *et al.*, 2007).

#### **Honey and chemotherapeutic drugs in combined therapy: supportive therapy**

Myelosuppression (bone marrow suppression) is the most important toxic side effect of most chemotherapeutic agents and typically is the dose limiting factor. Death occurring after chemotherapy usually results either from infection related to drug-induced leucopenia (7–14 days after the drug is administered) or from bleeding related to thrombocytopenia (Ozer *et al.*, 2000). Episodes of febrile neutropenia (FN, absolute lymphocyte count is less than  $700/\text{mm}^3$ ), a serious side effect of chemotherapy may result in subsequent chemotherapy delays or dose reductions. The use of colony-stimulating factors (CSFs) in patients with established neutropenia after chemotherapy is mostly routine in the primary and secondary treatment of patients

with grade 4 neutropenia. The incidence of transfusion-dependent anaemia induced by chemotherapy ranges from 9% to 40%. Treatment with recombinant human erythropoietin (rhEPO) increases haemoglobin levels, reduces transfusion requirements and promotes negative side effects. Administration of Life-Mel™ Honey (LMH) to prevent neutropenia and to reduce the need for CSFs was used in patients treated with chemotherapy (Zidan *et al.*, 2006). Thirty cancer patients receiving chemotherapy (cyclophosphamide + epirubicin + 5-FU, paclitaxel and carboplatin, gemcitabine, and single-agent taxanes as adjuvant or treatment for metastatic disease for primary or metastatic disease) had grade 4 neutropenia and were treated with CSFs. The patients repeated the same chemotherapy schedule, with the addition of LMH 5 g/d per o. s. for 5 days. It was deduced that LMH may be effective in decreasing the incidence of anaemia in 64% of the patients and in decreasing the incidence of severe neutropenia, even though 40% of patients required CSFs. The incidence of thrombocytopenia was also extremely low. One third of the patients reported improvement of quality of life during honey intake. No side effects were noted following honey intake. On the other hand, the cost of LMH for preventing neutropenia and anaemia was negligible when compared to that of treatment with CSF and EPOs, i.e., about 8% of the cost of CSFs for one course of chemotherapy.

Free radicals and reactive oxygen species (ROS) have been implicated in contributing to ageing and many disease states including cancer. It is known that cancer increases free radicals and that certain diets can influence oxidative stress. Thus, a diet of foods enriched with bioactive compounds may lead to significant effects on health and represents a promising adjuvant treatment in patients with advanced breast cancer, due to its contribution in lowering the high oxidative stress present in these patients (Drăgan *et al.*, 2007). The phenolic compounds contribute significantly to the antioxidant capacity of honey but are not solely responsible for it. Thus, honey may be used as a healthy alternative to sugar in many products and thereby serve as a source of dietary antioxidants (Gheldof *et al.*, 2002).

## The possible mechanism of action of honey

### Immunomodulation by honey

Numerous studies demonstrated that treatment with honey may stimulate macrophage activity to produce factors capable of regulating the function of B-, T- and NK-cells, respectively. Moreover, in healthy patient honey increased the percentage of monocytes by 50%, while lymphocyte and eosinophil percentages increased slightly (Al-Waili, 2003 a and b). It caused slight elevations in blood zinc and magnesium, haemoglobin, and packed cell volume. Honey reduced serum immunoglobulin E (34%), liver

and muscle enzymes, concentrations of prostaglandins (PGs) and fasting blood sugar levels in healthy subjects (Al-Waili, 2003a,b).

It is known that prostaglandins, nitric oxide (NO), free radicals and chronic inflammation play a major role in tumour-ogenesis. Tumours are associated with immunosuppression and anaemia. Al-Waili (2007) found that PGs suppress antibody production, reduce serum iron and modulate bone marrow function *in vivo*. It is possible that the reduction of prostaglandins may be an important factor in the stimulation of macrophages and other immune cells and improve the quality of life of patients with tumours. PG inhibitors have also been shown to be crucial in the prevention of tumours such as oesophageal and colon cancers. Inhibition of PGs can be achieved through the use of synthetic medicines and natural products such as honey and royal jelly (Bincoletto *et al.*, 2005). According to these results honey may be a promising modifier of biological response leading to myeloprotection and antitumour activity. It is also well established that PGE<sub>2</sub> exerts a negative feedback on macrophages (Goodwin and Webb, 1980) and that macrophages from tumour-bearing animals produced more PGE<sub>2</sub> than macrophages from normal mice (Pelus and Bockman, 1979). PGE<sub>2</sub> also modulates a variety of immune responses, including T-lymphocyte mitogenesis, lymphokine production, and macrophage- and NK cell-mediated cytotoxicity to tumour (Talmadge *et al.*, 1981). The immunosuppression may be directly induced by PGE<sub>2</sub> or this substance may induce T-suppressor cells (Fauve *et al.*, 1974; Snyderman and Pike, 1976). Immune responses of tumour bearers can occasionally be restored *in vivo* or *in vitro* by the treatment with prostaglandin synthesis inhibitors or by reducing systemic PGE<sub>2</sub> levels. Thus, interest in the use of honey as a PG inhibitor to prevent cancer and cardiovascular events is growing. In addition, it was reported that oral intake of honey augmented antibody productions in primary and secondary immune responses against thymus-dependent and thymus-independent antigens (Al-Waili and Haq, 2004).

Stimulating effects of honey on colonic probiotic bacteria may have a broad scope in general health interventions such as antimicrobial, immunomodulatory, and anti-carcinogenic, antiallergenic, antidiarrhoeal and antioxidant properties. The various mechanisms include chelation of metallic ions, scavenging of ROS, and reduction of bacterial activity (Oršolić and Bašić, 2008 a). They have been used for a wide variety of purposes such as managing lactose intolerance, for immunomodulation in chronic inflammatory and infectious conditions (vaginosis, candidiasis, and recurrent urinary tract infection), managing oral absorption syndromes, prevention of colon cancer, and for cardioprotection by lowering blood

pressure and cholesterol levels. Lactobacilli have been shown to produce biosurfactants and collagen binding proteins that inhibit pathogen adherence and displace the pathogens (Jassawala, 2007). Probiotics have multiple modes of action that are important to protect the damaged immune system after chemo- and radiotherapy:

- 1) they colonize and adhere to the colon and reinforce the barrier function of the intestinal mucosa helping in the management of intestinal infection and food allergies;
- 2) they secrete antimicrobial substances called bacteriocins;
- 3) they increase the levels of circulating immunoglobulins, especially immunoglobulin A;
- 4) they enhance the nonspecific immunophagocytic activity of circulating blood granulocytes;
- 5) they potentiate intestinal immune response to viral infection;
- 6) they increase the frequency of interferon, which stimulates the production and collection of peripheral blood monocytes;
- 7) they secrete proteolytic enzymes which digest bacteria toxins;
- 8) they alter the initiation and or promotional events of the chemically induced tumours by binding to the chemical carcinogen (Jassawala, 2007).

#### **Medical properties and mechanism of action of honey in wound healing process**

Normal wound healing is a complex process in which damaged tissue is removed and gradually replaced by restorative tissue during an overlapping series of events, which include coagulation, inflammation, cell proliferation, and tissue remodelling (Falanga, 2005). The inflammatory phase of healing has an essential role in clearing the wound site of infectious agents and debris; this is facilitated by the activity of innate immune cells such as neutrophils and macrophages, which migrate to the wound site in response to tissue damage (Martin and Leibovich, 2005). These cells aid the resolution of infection and removal of foreign material and cellular debris by phagocytosis (Martin and Leibovich, 2005). The individual role of neutrophils and macrophages has been investigated, and previous studies indicate that macrophages have an essential role in wound resolution (DiPietro, 1995), as the absence of macrophages leads to poor debridement of the wound site and delayed repair (Duffield *et al.*, 2005; Martin and Leibovich, 2005). In contrast, depletion of neutrophils leads to enhanced wound closure (Dovi *et al.*, 2003). In addition to their phagocytic role, macrophages release various growth factors and cytokines, which are important in perpetuating the healing process (Gillitzer and Goebeler, 2001). Recent studies indicate that production of IL-6 and TNF- $\alpha$  by macrophages and other cells at the wound site is essential in the healing process (Lin *et al.*, 2003; Zhang and Schluessener, 2006).

Honey facilitates an increase in lymphocytes and phagocytes and aids monocytes to release cytokines and interleukins (e.g.

TNF- $\alpha$ , IL-1 $\beta$ , IL-6), thus stimulating the healing process (Tonks *et al.*, 2003 and 2007). These events in myeloid cells are not a consequence of bacterial contamination of honey or lipopolysaccharides (LPS), a major component of the outer membrane of Gram-negative bacteria, but are specifically associated with a 5.8-kDa moiety isolated from manuka honey. Furthermore, this component stimulates inflammatory responses in monocytes via interactions with Toll-like receptor 4 (TLR4) (Tonks *et al.*, 2007).

#### **Present status and future prospects**

In the cancer setting, honey has been found to be effective for radiation-induced oral mucositis, stomatitis, periodontal, gum disease, radiotherapy-induced skin reactions, malignant ulcers, external surgical wounds and infected lesions in paediatric oncology patients (Bardy *et al.*, 2008). In addition, honey may be used to treat both fungating wounds and surgical wounds following the removal of tumours. It may be helpful in healing dry and moist desquamation wounds in radiotherapy-induced skin reactions. There might also be a role for honey in the treatment of chemotherapy-induced hand and foot syndrome (palmarplantar erythrodysesthesia), which is a skin reaction appearing on the palms of the hands and soles of the feet as a result of treatment with chemotherapy agents such as capecitabine or fluorouracil (Janusch *et al.*, 2006). Research could also be extended to include oral/oropharyngeal cancer patients postsurgically.

Topical application of honey may reduce both the severity and duration of radiation-induced oral mucositis and prevent weight loss. As the future multi-modality approach to cancer lies in chemo-radiotherapy and altered fractionation schemes, prevention of oral mucositis is very important in management. Complex wounds and wounds of immunocompromised patients should be treated only under professional medical supervision. Moreover, honey may also provide benefit in conventional oncological surgery where tumour implantation is predictable. However, metabolic effects of honey when used on large lesions are not known and need further investigation.

However, further randomised studies are essential to validate clinical evidence; a lack of consistency and use of grading criteria and reporting standards makes it difficult to draw comparative conclusions concerning toxicity end points among various trials. The lack of standardisation remains problematic, in spite of recent efforts to improve grading and reporting (Biswal, 2003). A further issue in the use of medicinal honey is quality assurance since natural honeys will vary between different geographic locations. The low water activity and acidic nature of honey make it a generally unsuitable medium for bacterial growth (Al-Waili, 2003; Molan, 2006). Nevertheless, a number of reports have described bacterial and

fungal contamination of honey (Blaser *et al.*, 2007; Simon *et al.*, 2009). This suggests contaminated honey may act as a potential source of infection. Indeed, honey has been identified as a source of botulism in infants (Molan, 2006; Simon *et al.*, 2009). The origin of these infectious agents in honey has been discussed in a previous review (Blaser *et al.* 2007) and includes the gut of honey bees and raw nectar. However, bacterial spores were isolated from approximately one-third of the samples; the majority of spores isolated in this study were *Bacillus* species, which correlates well with previous studies of bacterial contamination (Blaser *et al.*, 2007). The presence of bacterial spores raises the possibility that honey samples may be contaminated with bacterial components including LPS, which may be responsible for the cytokine -inducing activity of the honey. From a professional medical perspective, honey used in wound care should have a proven antibacterial activity against the most important pathogens in wound infection (*S. aureus*, *Pseudomonas aeruginosa*) (Blaser *et al.*, 2007) measured with an appropriate microbiological *in vitro* method (Mullai *et al.*, 2007; Irish *et al.*, 2006). In addition, it should be irradiated especially if it is used in deep or partially necrotic wounds (Yapucu Gunes and Eser, 2007).

In the near future, an internet-based documentation system with standardized items for the documentation of wound healing in patient treated with honey will be available. The main objective of this database will be the cumulative analysis of prospectively documented treatment experiences from many centres. The results will be sent to the participating centres and published in the medical literature (Simon *et al.*, 2009).

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