Honey in Anticancer Drug Toxicity

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Abstract

Cancer is a major health issue and the second leading cause of mortality in the world. The most common treatment of cancer is chemotherapy, but adverse effects and chronic sequelae developing from anticancer chemotherapy hamper its clinical use despite its efficiency and adds to the discomfort of cancer patients. The side effects, however, are different for different people depending upon health, dosage and the type of cancer. The most common types of toxicities induced through chemotherapeutic drugs are oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, cardiotoxicity, and neurotoxicity. Natural products are known for a number of properties, one being prevention and treatment of drug toxicities in cancer. Natural honey is a combination of phenolic acids, flavonoids, antioxidants, etc. and acts as a chemoprotectant and adjuvant during cancer treatment. This book chapter focuses in detail on the efficiency of honey from a potential therapeutic perspective and explains the possible mechanisms of the actions in increasing the tolerance and treatment of chemotherapy-induced side effects in clinical settings. In addition, particular attention is drawn to the role of chrysin, which is a honey flavonoid used in protection against drug therapy-induced toxicities.

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Keywords

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14.1 Introduction

Globally, the most common cause of death is cancer (Bray et al. 2018). Chemotherapy and radiotherapy are the most effective and extensive approaches for cancer management. However, chemotherapy and radiotherapy-induced feared side effects including oral mucositis, gastrointestinal toxicity, nephrotoxicity, hepatotoxicity, cardiotoxicity, neurotoxicity and myelosuppression are not only the major concerns for patients but for clinicians as well as they may hinder the clinical usage despite boosting the survival (Shapiro 2016). Even natural chemotherapeutic agents with epirubicin, taxol and irinotecan also result in various problems including bone marrow depression. Half of the cancer patients get mucositis on chemotherapy and more than 50% when chemotherapy is combined with radiotherapy. These harmful side effects along with emotional and psychological stress often worsen the quality of life in cancer patients, and may lead to treatment termination (Ahmed and Othman 2013). Effective management approaches are necessary to increase tolerance for chemotherapy-induced side effects that would lessen the severity. There is increasing evidence that many natural products tend to decrease the side effects resulting from such treatments and may be useful when used together to inhibit overproliferation in tumours by cell cycle arrest and prevent metastatic invasion and stimulation of programmed cell death via activating pathways that increase the expression of tumor necrosis factor alpha (TNF-α) and as well as cause inhibition of lipoprotein oxidation. Natural products may be effective against toxic agents in in vitro and animal experiments (Sanders et al. 2016). Honey has been regarded as one of the natural products that mediates these beneficial effects along with its components. Honey has been used since medieval times as a nutritional product and mainly for its remedial and therapeutic significance in traditional medicine (Braakhuis et al. 2019). It has been shown to have anticancer, anti-inflammatory, antibacterial, antiviral, antidiabetic, antimutagenic and antioxidant properties (Erejuwa et al. 2010; Kishore et al. 2011; Viuda Martos et al. 2008). Honey also has the same antitumor activities as some of the chemotherapeutic drugs. Many types of honey are available worldwide but its chemical and physical composition varies from one place to another depending upon the flora source, season, environment, and geographical origin as well as honeybee species. Honey is a natural liquid consisting of at least 181 ingredients including proteins, minerals, vitamins and natural organic acids (Al-Waili et al. 2012). Honey also contains phenolic acids like caffeic, ferulic, ellagic and coumaric acids; flavonoids such as apigenin, chrysin, galangin, hesperetin, kaempferol, pinocembrin and quercetin; antioxidants, such as tocopherols, ascorbic acid, superoxide dismutase, catalase and glutathione and glycosides, quinone, alkloids, cardiac glycosides, and volatile substances (Grecka et al. 2018). All these constituents have their unique properties and together they

increase the dietetic and homeopathic value of natural honey (Vit et al. 2015). Honey has high content of bioactive plant compounds and various constituents of honey have antioxidant properties as well. Flavonoids such as chrysin in honey have a strong antioxidant property and are present in large content (Islam et al. 2017). According to the recent scientific literature, honey and chrysin may be effective against a wide range of diseases from wound healing to cancer (Lavaf et al. 2017; Song et al. 2019; Yuan et al. 2019) and both play a role in preventing natural and chemical toxicity in different tissues (Van Meeuwen et al. 2007). Several studies have suggested that honey and its components decrease neurotoxicity, lung toxicity, cardiovascular toxicity, hepatotoxicity, nephrotoxicity, reproductive toxicity, genotoxicity and immunotoxicity by modulating oxidative stress and apoptosis in various organs. Drug toxicity is one of the main problems concerned with chemotherapy and causes various illnesses (Nurgali et al. 2018). Honey is suitable and effective for the treatment of oral mucositis and skin reactions, stomatitis, periodontal gum disease, malignant ulcers, external surgical wounds, infections in paediatric oncology patients and chemotherapy-induced palmar-plantar erythrodysesthesia or hand-foot syndrome. It is a dermatologic reaction on the skin of hands and feet caused due to cytotoxic chemotherapy drugs such as fluorouracil or capecitabine (Janusch et al. 2006). Therefore, more clinical studies should be done to confirm the efficacy and safety of honey and chrysin for treating chemotherapy based intoxication. Thus, this book chapter aims to review the protective effects of honey against chemotherapy-induced drug toxicity.

14.2 Chemotherapy-Induced Damages and Honey

The use of either fresh, old or raw natural bee honey has been shown to be effective in the management of various problems caused after chemotherapy such as mucositis, infections such as throat infection, vomiting, diarrhea, constipation and many more (Maiti et al. 2012). Oral mucositis is one of the most significant oral cavity complications in patients undergoing chemotherapy or radiotherapy or a combination of both that triggers ulceration of oral mucosa, painful oral lesions, erythema and systemic infections. This can result in prolonged hospitalization and decreased chances of cure. Most of the cancer patients receiving intensive chemotherapy suffer from this dose limiting complication that significantly affects the patients with malignancies in the head and neck (Simon et al. 2009). Clinical evidence demonstrates that honey can treat the cytotoxic effects of mucositis in children, hence used as a therapeutic measure in paediatric cancer patients (Friend et al. 2018). In a pilot study on patients with acute lymphoblastic leukemia and a condition of oral mucositis, honey alone and a combination of honey, olive oil, propolis and beeswax (HOPE) showed that topical treatment of honey or HOPE resulted in faster healing as compared to the control group, hence both having a role in chemotherapy-induced mucositis (Abdulrhman et al. 2012). A study compared the role of honey + coffee in the treatment of mucositis and found that as compared to betamethasone-treated (steroid) and honey-treated groups, the honey + coffee group

showed significant reduction in the severity of lesions in the hypopharynx mucosal membrane. This may be due to the fact that caffeine in coffee has anti-inflammatory and antioxidant effects on a number of tissues and together with honey it synergistically increases mucosal tissue healing (Raeessi et al. 2014). A study on children suffering from chemotherapy-induced mucositis showed confirmed positive effects and the simple, cost-effective modality role of honey in the management of oral mucositis. As compared to the control group that received antiseptic gel treatment, the experimental group received additional treatment with honey. The latter group showed reduced severity and rapid management of mucositis (Singh et al. 2019). Combinational therapy with the use of honey and tulsi (*Ocimum tenuiflorum*) ice chips together with chemotherapy was found to be superior to chemotherapy alone due to the fact that this treatment before the dose of methotrexate in children showed decreased signs of mucositis (Mishra and Nayak 2017). A study showed the chemopreventive role of Yashtimadhu (*Glycyrrhiza glabra*) together with honey in head and neck malignancies after receiving therapy and that the intensity of mucositis and skin reactions was reduced when this combination was used either orally or locally (Das et al. 2011). A similarly combination of glycerine plus honey in oropharangeal cancer patients showed delayed occurrence of mucositis compared to the control group receiving the standard treatment (Bansal et al. 2017). In patients with oral cancer, which is more common in India, topical application of honey was found to have a contending role in preventing the side effects of chemoradiation-induced mucositis like dysphagia, irritation and dryness as well as helping in speedy recovery (Howlader et al. 2019). Propolis is a resinous mixture found in honey and has anti-ulcer, anti-microbial, healing and anti-inflammatory properties. In a clinical trial, Hypozalix spray and propolis mouthwash efficiently decreased the occurrence of and healed oral mucositis in patients with head and neck malignancies or leukemia (Eslami et al. 2016). In a similar meta-analysis study and propolis mouthwash was found to be an effective and safe treatment (Kuo et al. 2018). Propolis extract was given to patients with breast cancer receiving adjuvant therapy with doxorubicin and cyclophosphamide and was found to prevent the occurrence of mucositis (Piredda et al. 2017). Oral mucositis is caused by pathogens like bacteria, and honey is known for its antibacterial properties against a wide range of bacteria. Its bioactive compounds and components like hydrogen peroxide and the bee-derived antibacterial peptide defensin-1 are majorly known to be responsible for its antibacterial activity. However, due to variation in the concentrations of these compounds, different types of honey show different levels of inhibition (Bucekova et al. 2019). The antibacterial role of honey against *Candida* and aerobic pathogenic bacterial infections showed reduction in the onset of mucositis in pediatric cancer patients when applied topically, hence can be used as a prophylaxis (Al Jaouni et al. 2017). Standard or high-dose cytarabine (Ara-C) has been shown to develop chemotherapy-induced gastrointestinal complications like abdominal pain and diarrhea and together with fever and melena may cause a life threatening condition in acute myeloid leukemia (AML) patients undergoing chemotherapy. There is high incidence of ileothyphlitis and other gastrointestinal infections (28.5%) in such patients as well (Micozzi et al. 1996). In such patients with gastrointestinal

complications, the effect of the combination of honey and ardeh favoured recovery from side effects vs. control. Also, it reduced fever, neutropenia nausea and vomiting in patients with acute myeloid leukemia significantly (Ebrahimi et al. 2016). All therapeutic routines produce varying side effects, including haematological toxicity. The most toxic side effect of the majority of chemotherapeutic agents is myelosuppression (bone marrow suppression) and classically is the dose-limiting factor. It can vary in its severity from mild to severe. A severe type of myelosuppression, called myeloablation, can be lethal. With myelosuppression there can be a decline of some or all of the body's bone marrow producing cells like the red blood cells, white blood cells and platelets. The administration of different chemotherapeutic agents and even those of natural origin, such as epirubicin, irinotecan and taxol causes toxicity in the precursor cells of bone marrow, hence causing early bone marrow depression which is characterized by rapid cell division (Oršolić et al. 2005; Oršolić and Bašić 2008). Febrile neutropenia is a condition that results from systemic chemotherapy and causes opportunistic infections in cancer patients subsequent to chemotherapy. Colony-stimulating factors (CSFs) are known to treat patients with neutropenia by acting as an adjuvant. Administration of Life-Mel honey instead of CSFs in patients treated with chemotherapy decreased the risk of pancytopenia. On administration of honey along with the same chemotherapy schedule there was no need of CSFs in 40% of the patients with no side effects. This treatment proves to be inexpensive, easy and costs only 8% of the CSF course in chemotherapy (Zidan et al. 2006). After chemotherapy the cause of death can be either the infectivity related to drug-induced leucopoenia or from hemorrhage related to thrombocytopenia (Ozer et al. 2000). Similarly, in children with acute lymphoblastic leukemia intake of raw honey of about 2.5 g/kg given twice a week for 12 weeks was considered safe against the adverse effects of chemotherapy-induced febrile neutropenia (Abdulrhman et al. 2016). Honey in combination with chemotherapeutics (5-FU or adriamicin) may prevent chemotherapeutic-induced toxicity on leukocyte populations in the peripheral blood (Orsolic and Basic 2004). *Cis*-diamminedichloroplatinum is a potent drug used in chemotherapy against broad-spectrum tumors but has nephrotoxic side effects. A study was carried out in Wistar rats where bee honey, royal jelly and cisplatin were given to different groups to check the nephroprotective effects of natural products, honey and royal jelly on renal injury. Cisplatin treatment was given beforehand and unlike this group the honey- and royal jelly-treated group showed normal serum biomarkers for renal injury and low expression of transforming growth factor β1, α-smooth muscle actin and bromodeoxyuridine (Brdu) (Ibrahim et al. 2016). Similarly, the nephroprotective effects of honey and royal jelly were seen in cancer patients receiving cisplatin in chemotherapy, which showed promising results (Osama et al. 2017). In a rat model, the role of Manuka and Talh honeys was assessed on cisplatin-induced nephrotoxicity and hepatotoxicity and both showed protective effects by limiting the inflammatory and apoptotic pathway (Neamatallah et al. 2018).

14.3 Honey and Its Components: Chemoprevention and Adjunct to Anticancer Drugs

The chemopreventive role of honey and its components to combat the negative side effects of cancer treatments has been shown to improve the quality of life for patients with variety of cancers. Similarly, the role of honey as an adjuvant with drugs during cancer therapies is shown to prevent progression to malignancy, reduce the required dosage of conventional drugs, lessen the severity of adverse effects and help in the management of cancer therapy overall (Table 14.1). 5-fluorouracil (5-FU) is one of the frequently used chemotherapy drugs against a wide range of cancers including colorectal cancer, and it exerts it anticancer property through inhibition of thymidylate synthase. A study was performed to see the impact of a combined treatment of ginger extract and honey with 5-FU on inhibition of cell growth and cell death, i.e. the chemotherapeutic effect of 5-FU. It was shown that in comparison to the treatment of cells with ginger extract and Gelam honey alone, the co-treatment of Gelam honey and ginger extract with 5-FU shows a higher rate of anti-proliferative effects on cancer cells. It was three times higher than that with 5-FU treatment alone due to a synergism between the ginger extract and the Gelam honey in a dose-dependent manner (Hakim et al. 2014). To unravel the signaling pathways involved during such combination treatments in anticancer mechanism have not been extensively studied. However, in one study on colorectal cancer (HT29) cell line, the cells were treated with ginger extract and Gelam honey in independent and combined therapy. It showed a synergism between the two compounds for curbing the proliferation and activation of apoptotic pathways through increased expression of caspase 9 and IκB genes and decreased expression of KRAS, extracellular-signal-regulated kinase, protein kinase B (Akt), B-cell lymphoma-extra large (Bcl-xL) and NF-κB (p65) genes (Tahir et al. 2015). Another similar study showed the effect of synergism between ginger extract and Gelam honey on colon cancer (HCT116) cells. The effect was seen on various pathways like mTOR, Wnt/β-catenin and apoptosis signaling pathways. The combined therapy down-regulated the expression of mTOR, Raptor, Akt, Rictor, Gsk3β, β-catenin, Tcf4 and cyclin D1 genes, while cytochrome C and caspase 3 genes were up-regulated (Wee et al. 2015). Similarly, the effect of Manuka honey on enhancing the anticancer property of 5-FU on human colon cancer HCT-116 cells and LoVo cells showed a synergistic role in diminishing cell growth through suppression of the epidermal growth factor receptor (EGFR), HER2, p-Akt and p-mTOR expression and transcription factor (NF-κB and Nrf2); increasing cell death by modulation of pro-apoptotic markers like p53, Bax, Cyto c, FasL caspase-3, -8, -9, cleave-PARP and anti-apoptotic Bcl-2 marker; decreasing antioxidant enzyme activity (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) and suppressing the expression of metalloproteinases-2, 9 and increasing N-cadherin and E-cadherin in metathesis. Manuka honey acts as an adjuvant in the treatment of colon cancer (Afrin et al. 2018). The phytochemical content and the antioxidant activity of Strawberry tree honey and Manuka honey on human colon adenocarcinoma (HCT-116) and metastatic (LoVo) cell lines were compared and both the Strawberry tree honey and Manuka honey showed an

Table 14.1 Chemo protective effects of honey and its components against toxic agents and honey as an adjuvant to anticancer drugs

Honey	Toxic agents	Function	Cancer type	References
Ginger extract and Gelam honey	5-fluorouracil	Inhibition of thymidylate synthase	Colorectal Cancer	Hakim et al. (2014)
Manuka honey	5-fluorouracil	Suppression of EGFR, HER2, p-Akt and p-mTOR, NF-κB, Nrf2, SOD, CAT, GPx, glutathione reductase, MMP-2, MMP-9 and Bcl-2, activation of p53, Bax, Cyto c, FasL caspase-3, -8, -9 and cleave-PARP, and N-cadherin and E-cadherin	Colorectal Cancer	Afrin et al. (2018)
Manuka honey	Paclitaxel	The rate of apoptosis in tumor cells was alleviated	Melanoma mice	Fernandez-Cabezudo et al. (2013)
Tualang honey Manuka honey	*N*-methyl-*N*-nitrosourea	Manuka honey more effective in inhibiting tumor growth than Tualang honey	Breast cancer	Othman et al. (2016)
Tualang honey	7,12-dimethylbenz (α)anthracene	Tumour size, histological grade, VEGF levels and angiogenesis were decreased	Breast carcinogenesis	Kadir et al. (2013)
Tualang honey	Tamoxifen	Inducing the apoptosis on ER responsive MCF-7 and ER non-responsive MDA-MB-231 cells	Breast cancer	Yaacob et al. (2013)
Tualang honey	4-hydroxytamoxifen	Tualang honey was cytotoxic to MCF-7 and not to normal MCF-10A cells	Breast cancer	Yaacob and Ismail (2014)

(continued)

Table 14.1 (continued)

Honey	Toxic agents	Function	Cancer type	References
Sunflower honey	Tamoxifen and aromatase inhibitors	Reduced the menopausal complaints	Breast cancer	Münstedt et al. (2015)
Honey	Cisplatin, cyclophosphamide and 5-fluorouracil	Decreased the activity of sera ALT, AST and ALP and increased activities of CAT, SOD, GPx, GST and GSH	Liver hepatocarcinogenesis	Mohamed et al. (2019)
Honey	Diethlynitrosamine	Less lesions and less damaged hepatocytes, edema and malignancy	Hepatocellular carcinoma	El-Kott et al. (2012)
Kelulut honey	Azoxymethane	Crypt foci, multiplicity and total aberrant crypts were reduced	Colon cancer	Saiful Yazan et al. (2016)
Iranian propolis	*N*-methyl-*N*-nitro-*N*-nitrosoguanidine	Smaller gastric lesions and a decline in structural abnormality, epithelial stratification and nuclear dispolarity	Gastric cancer	Dinparast-Djadid et al. (2015)
Propolis, caffeic acid, wild flower honey, royal jelly and bee venom	Methylcholanthrene	Honey has antimetastatic effects and less significant tumour nodules in the lungs	Transplantable mammary carcinoma and methylcholanthrene-induced fibrosarcoma	Oršolić et al. (2005)

increased rate of cell death, cytotoxicity in both cancer cell lines as compared to non-cancer cells. In addition, there was an increase in the generation of reactive oxygen species (ROX) by Strawberry tree honey and Manuka honey in HCT-116 and LoVo cells as well. These results suggest a potential chemopreventive agent against colon cancer, and honey can act as an adjuvant in the functioning of drugs already used in cancer treatment (Afrin et al. 2017; Badolato et al. 2017). Manuka honey administration with the antineoplastic drug paclitaxel alleviates the chemotherapy-induced cytotoxicity in the melanoma model of mice (C57BL/6). The study was carried out where mice were administered with Manuka, paclitaxel

or a combination of both. After treatment, the rate of apoptosis in tumor cells was found to be the highest in mice treated with a combination of Manuka and paclitaxel (Fernandez-Cabezudo et al. 2013). In the breast cancer-induced rat model, Tualang and Manuka honey were administered after induction of breast carcinogenesis with *N*-methyl-*N*-nitrosourea. Manuka honey was shown to be more effective in inhibiting the tumor growth than Tualang honey (Othman et al. 2016). But a study on Tualang honey showed that it could be used as an adjuvant in chemotherapy in breast carcinogenesis. On administration of Tualang honey, the size of breast tumor induced by the carcinogen 7,12-dimethylbenz(α)anthracene (DMBA) in rats was reduced as compared to controls (not treated with honey). Many other factors were also reduced like histological grade, VEGF levels and angiogenesis. However, the apoptotic index was high in the honey treated cancer group but in general the average AI was the same for both the TH group and non-TH-treated group (Kadir et al. 2013). Tamoxifen is a drug used as an adjuvant for chemotherapy in women with high susceptibility for breast cancer. Its various toxic side effects were reduced in combination with Tualang honey on healthy cells, non-tumour breast cancer cell line (MCF-10A). Similarly, on estrogen receptor (ER) responsive (MCF-7) and ER-non-responsive human breast cancer (MDA-MB-231) cell lines, Tualang honey increased the effectiveness of the drug tamoxifen by inducing apoptosis on both MCF-7 and MDA-MB-231 cells compared to independent treatments (Yaacob et al. 2013). Similarly, a study showed the effect of Tualang honey on cancerous MCF-7 cells in comparison to normal MCF 10A cells independently and in combination with 4-hydroxytamoxifen, an active metabolite of tamoxifen. 4-Hydroxytamoxifen was cytotoxic to both cell lines, while honey was cytotoxic only to MCF-7 and not to MCF-10A. Tualang honey increased the 4-hydroxytamoxifen-induced DNA damage on MCF-7 cells but decreased the toxic effect of 4-hydroxytamoxifen by increasing the expression of DNA repair proteins Ku70 and Ku80 in MCF-10A cells (Yaacob and Ismail 2014). In patients with breast cancer, Sunflower honey was given along with tamoxifen and aromatase inhibitors that reduced the menopausal complaints in patients with breast cancer (Münstedt et al. 2015). Liver hepatocarcinogenesis is the second cause of cancer-related deaths. The combinational therapy of honey and chemotherapeutic drugs and honey alone has been very effective in chemoprevention against diethylnitrosamine and carbon tetrachloride-induced hepatocellular carcinoma in rats. The chemotherapy drugs used in this study are cisplatin, cyclophosphamide and 5-fluorouracil. These drugs show decreased activity of sera alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) but the induction was more potent in case of treatment with honey plus drugs. Similarly, the co-administration showed a significantly higher increase in the activities of antioxidant enzymes of catalase, superoxide dismutase, glutathione peroxidase, glutathione-*s*-transferase and glutathione as compared to the control (Mohamed et al. 2019). In a study, hepatocellular carcinoma was induced in Sprague Dawley rats through diethlynitrosamine administration, which is considered a liver carcinogen. The groups treated with honey and diethlynitrosamine alone and in combination showed a different liver histology. The liver hepatocytes of the groups treated with diethlynitrosamine + honey and honey alone were normal,

while those treated with diethlynitrosamine had lesions and damaged hepatocytes, edema and malignancy. Also, P-53 tumor protein and proliferating cell nuclear antigen (PCNA) positive nuclei were observed more significantly in immunohistochemistry liver sections for the diethlynitrosamine group than the diethlynitrosamine + honey group and no expression was observed in controls (untreated and honey groups). This indicates honey as a therapeutic agent in hepatocellular carcinoma (El-Kott et al. 2012). Cisplatin is one of the most common chemotherapeutic drugs used for tumors but is known for nephrotoxicity. This study showed that honey protects the kidneys from nephrotoxicity of cisplatin by improving the kidney function, reduces cisplatin-induced tubular epithelial cell death, reduces inflammation in the kidneys and decreases proinflammatory cytokine and chemokine activation such as NF-kB. For this the animals were first treated with orally administered crude honey 500 mg/kg per day for a week followed by cisplatin (Hamad et al. 2015). Another study showed the therapeutic role of *Schisandra chinensis* bee pollen extract (SCBPE) on liver and kidney injury induced by cisplatin (Huang et al. 2017). Kelulut honey produced by the stingless bees from Trigona species is known for its chemopreventive properties. In a study colon cancer was induced in Sprague Dawley rats with azoxymethane administered through the intraperitoneal route. Honey was administered twice orally for 8 weeks followed by azoxymethane that was given once a week for 2 weeks to the treated group, while others were azoxymethane alone, honey alone and untreated control groups. The blood profile and the kidney and liver function for all the groups were similar. However, the aberrant crypt foci, multiplicity and total aberrant crypts were reduced on treatment with kelulut honey, hence overall it is chemopreventive and non-toxic (Saiful Yazan et al. 2016). Propolis is found in honey and has a number of properties including anticancer. Iranian propolis was shown to have a protective effect on *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG)-induced gastric cancer. Propolis was administered before the induction in animals followed by assessment for metastatic tumors and expression of apoptotic genes. As compared to control, the MNNG + propolis-treated group showed smaller gastric lesions by 33%, the number of tumors was reduced by 38% and there was a decline in structural abnormality, epithelial stratification and nuclear dispolarity. Similarly, immunohistochemistry showed increased expression of pro-apoptotic Bax protein and decreased expression of anti-apoptotic Beta-catenin and Bcl-2 in the MNNG + propolis group as compared to the group treated with MNNG only (Dinparast-Djadid et al. 2015). The anti-metastatic and anti-tumour properties of propolis, caffeic acid, wild flower honey, royal jelly and bee venom were examined in the transplantable mammary carcinoma (MCa) model and methylcholanthrene-induced fibrosarcoma mouse models. Honey administration before and after tumor inoculation showed anti metastatic effects and less significant tumour nodules in the lungs. Similarly, propolis and caffeic acid showed significant protective effects before and after tumour inoculation. Royal Jelly showed no protective effects before and after tumour inoculation but showed a significant role in inhibiting the tumour when inoculated together with tumour cells (Oršolić et al. 2005). Cyclophosphamide is a cytotoxic alkylating agent used in treating a number of problems like cancer, autoimmune diseases, etc. and its two

active products are phosphoramide mustard and acrolein, both being highly toxic. A study was carried out to examine the effects of honeybee products such as propolis, royal jelly and pollen grains on a cyclophosphamide-induced tumor model and was found to ameliorate the side effects of the anticancer drug cyclophosphamide (Fahmy et al. 2015). In mice and human bladder cancer cell lines, bee honey reduced the cell number with an increase in the concentration of honey, increased the apoptotic index as compared to controls and decreased cell proliferation than in the untreated cells. Also, oral and intralesional injection of honey showed a decrease in the volume of subcutaneously implanted abdomen tumours in mice treated with honey than in the untreated controls (Swellam et al. 2003).

In future, studies should be commenced to validate the role of varieties of honey and its components, which will have remarkable clinical implications in cancer treatment.

14.4 Role of Chrysin in Drug Toxicity

Chrysin is a flavonoid that occurs naturally in bee propolis and honey and is one of the phytochemicals known to have a wide range of health benefits (Siddiqui et al. 2018; Cheung et al. 2019). It provides protective effects from toxicities caused by various chemotherapeutic drugs in various tissues including the liver, kidneys, heart and lungs (Fig. 14.1) and has pharmacological activities like inhibition of nitric oxide synthase, NF-κB, histone deacetylase and DNA topoisomerases, and anti-inflammatory role by preventing the release of pro-inflammatory cytokines, anticancer role by inducing apoptosis, activation of TNF related apoptosis-inducing ligand (TRAIL), inhibition of TNF-α and IL-1β and antidiabetogenic, antimetastatic and antihypertensive roles (Samarghandian et al. 2017, 2019). Chrysin has protective roles against various chemotherapeutic drugs that induce hepatotoxicity such as methotrexate and cisplatin. Methotrexate is a chemotherapeutic drug used in the treatment of a wide range of tumours and autoimmune diseases but its hepatotoxic effect on the liver limits its clinical use. It exerts its side effect by generating oxidative stress through reactive oxygen species (ROS). Both normal and cancerous cells are subjected to ROS-induced apoptosis. The antitoxic role of chrysin was demonstrated in a study on male wistar rats. Chrysin was given at different dosages and showed anti-hepatotoxic and anti-apoptotic effects through its free radical scavenging property. The chrysin pretreatment group showed normal liver function, the hepatocytes were normal and less distorted. The toxicity markers in the serum like lactate dehydrogenase, alanine transaminase and aspartate-aminotransferase and protein expression of apoptotic markers like p53, Bax protein and caspases 3 were reduced in the chrysin-treated groups and elevated in the methotrexate-treated group. Chrysin also modulates the enzymatic activity of superoxide dismutase and catalase, which are the main antioxidants (Ali et al. 2014). Cisplatin exerts its cis-induced hepatotoxic role through inflammation and oxidative stress. Oral treatment of chrysin in wistar rats pretreated with cisplatin prevented lipid peroxidation, xanthine oxidase activity and glutathione depletion. Chrysin prevented hepatic tissue damage,

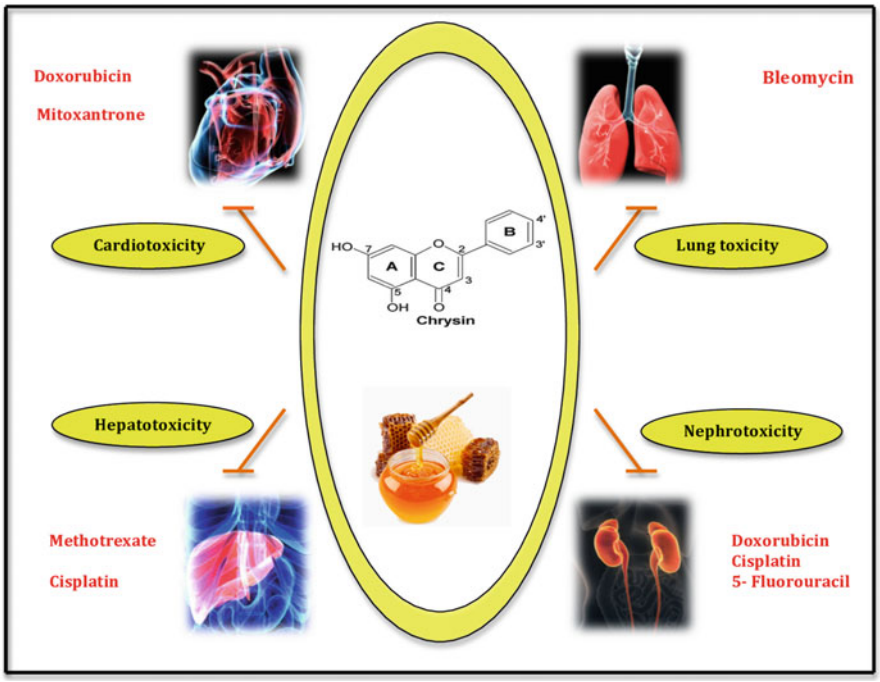

Fig. 14.1 The protective effect of chrysin against chemotherapeutic drug-induced toxicities of the heart, lungs, liver and the kidneys

enhanced expression of cyclooxygenase-2, iNOS and NF-κB, and TNF-α levels (Rehman et al. 2014). Chrysin also has a protective role in cisplatin-induced jejunal toxicity by decreasing the levels of antioxidant enzymes such as catalase, glutathione reductase, glucose-6-phosphate and dehydrogenase and phase II detoxifying enzymes (glutathione-*S*-transferase and quinone reductase) and glutathione, increasing xanthine oxidase activity and attenuating the expression of p53 and apoptotic tissue damage induced by cisplatin (Khan et al. 2012). Chrysin also provides protection against 1,2-dimethyl hydrazine carcinogenesis-induced rat model by reducing preneoplastic colorectal lesion numbers, increasing antioxidant activities and decreasing proliferation and stress (Sequetto et al. 2013). Chrysin plays a protective role against chemotherapy agent-induced cardiotoxicity such as doxorubicin and mitoxantrone. Mitoxantrone treatment causes irreversible congestive heart failure and cardiomyopathy that reduces the left ventricular ejection fraction. It increases the levels of cardiac injury indicator, creatine kinase (CK-MB) and pro-apoptotic markers Bax and caspase-3, while decreases the Bcl-2 expression. Chrysin treatment prevented apoptosis though a decrease in the Bax/Bcl-2 ratio, restoration of desmin disarray (Anghel et al. 2015). Doxorubicin induces cardiovascular toxicity through generation of inflammation, apoptosis and oxidative stress (Minotti et al. 2004). Chrysin was shown to prevent such side effects through

decreasing the pro-apoptotic activity of Bax and cytochrome c and caspase-3, reduced expression of COX-2, NF-κB, iNOS, and the levels of TNF-α and NO and increasing the activity of Bcl-2, antioxidant enzymes (catalase and superoxide dismutase) and lipid peroxidation (Mantawy et al. 2014). Doxorubicin also induces renal toxicity via decreased antioxidant activities. Chrysin prevents nephrotoxicity by managing the levels of aspartate aminotransferase, alanine transaminase and lactic acid dehydrogenase and reversing the histopathological damages (Rashid et al. 2013). Cisplatin is also known for inducing nephrotoxicity through oxidative damage by increasing the antioxidant enzyme (catalase, glutathione peroxidase, glutathione reductase and glutathione S transferases) expression and diminishing markers like serotonin and blood urea nitrogen (Sultana et al. 2012). Cardiovascular toxicity, liver toxicity and renal toxicity by 5-fluorouracil, an antineoplastic drug, limits its clinical use. It causes side effects like apoptosis and oxidative stress in the kidneys through activation of pro-apoptotic proteins and decreases the expression of anti-apoptotic proteins. Administration of chrysin after induction of rats with 5-FU showed a marked decrease in toxicity markers, regulated apoptosis in the kidneys and restored renal histoarchitecture, tubular architecture, etc. (Rashid et al. 2014). In respiratory toxicity, chrysin protects against bleomycin in rats by reversing alveolar congestion and connective tissue infiltration and reducing activities of catalase, superoxide dismutase and glutathione and lung inflammation and fibrosis (Kilic et al. 2014). Since most of these studies are based on animal models, more studies and human clinical trials are required to establish the role of chrysin in human toxicities.

14.5 Conclusion

This book chapter summarizes the role of different types of honey in preventing side effects caused by drugs used in chemotherapy. Conventional honey is shown to have chemo protective effects against chemotherapy-induced mucositis, myelosuppression, nephrotoxicity and neutropenia. Since honey is a combination of various bioactive compounds like phenolic acids, flavonoids and antioxidants, in future many studies are required to identify the role of each component in honey responsible for the prevention of chemotherapy-induced damages. Chrysin is one of the most extensively studied flavonoid that has multiple roles in various diseases and is known for its role in preventing toxicities in the liver, lungs, heart and kidneys induced by chemotherapeutic drugs given during cancer treatment. Since a majority of the studies are based on animal models, human clinical studies are necessary to establish its role. More clinical trials are needed to prove the authenticity of honey treatment either alone or as an adjuvant to understand the role of honey in cancer. Also due to allergic reactions associated with bee products found in honey in different concentrations like bee pollen, propolis and royal jelly, more research is needed to find the appropriate intake dosage for developing them in a potent apitherapeutic agent that can provide health benefits.

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