Chapter 35
Use of Honey in Cancer Prevention and Therapy

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This chapter is dedicated to cancer sufferers and survivors, and researchers engaged in its prevention and therapy

35.1 Introduction

The typical composition of honey (Codex Alimentarius Commission 2001) provides a generalization that misses variability in composition of an apparently homogeneous sugary product. Therefore, it was referred to as enigmatic honey in a book on melissopalynology (Vit 2005) meaning honey not being a standard syrup. Commonality and variability in properties of honey is considered to be useful in making informed healthcare choices (Gethin 2008). Honey composition and other factors may readily explain this variability, as shown in several chapters in this book.

Variability in either composition of honey and characteristics of cancer raise a question: what type of honey for what cancer, at what stage of the disease, and in what dosage and timing? Further questions arise on the usefulness of honey intake alone or as an ingredient of natural remedies, or used in combination with conventional chemotherapy. Honey alone showed moderate murine antitumor activity and pronounced antimetastatic effects, but combined with anticancer drugs, 5-fluorouracil and cyclophosphamide, resulted in antitumor activity (Gribel and Pashinkii 1990). The use of honey with *Aloe arborescens* has been associated with tumor regression and survival time in patients

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treated simultaneously with oncologic chemotherapy (Zago 2004; Lissoni et al. 2009). In a review of 131 studies, *Aloe vera* and honey prevented or reduced mucositis, varying with the type of cancer and treatment (Worthington et al. 2010). *Aloe vera* and honey were hepatoprotective, reduced cell proliferation, and increased apoptosis in murine tumors (Tomasin and Gomes-Marcondes 2011).

Two recent reviews covered the ethnopharmacological uses of honey in north-eastern Brazil, with a number of stingless bee species (*Melipona scutellaris*, *Melipona subnitida*, *Partamona seridoensis*, *Scaptotrigona* sp., and *Tetragonisca angustula*) (Oliveira et al. 2010; Souto et al. 2011). However, the term cancer was not included as a disease descriptor. Possibly cancer as such cannot be diagnosed in traditional medicine, but can only be related to inflammations and swellings.

Cancer, the most dreaded disease of our time, is curable if detected in its early stages (Cantor 2008). The use of honey in cancer prevention and therapy has been tested both in vitro and in vivo, but the data do not cover the range of honey types or cancer symptoms known to exist. A number of cellular pathways in diverse cancer cell lines that are being investigated may eventually lead to a unified concept applying to the plethora of diseases termed cancer. The apoptotic ability (anti-proliferative potential, arresting cell growth at the subpopulation sub-G_1, activation of the caspase cascade) of honey varies according to the cell type, e.g., in colon cancer cells (Jaganathan and Mandal 2009b), and involves nonprotein thiols, mitochondrial dysfunction, reactive oxygen species, and protein p53 (Jaganathan and Mandal 2010). The group of Nada Oršolić at the University of Zagreb in Croatia demonstrated growth inhibition of certain tumor types, reduction of metastases and prolonged survival in mice, after treatment with honey alone (Oršolić 2009), or propolis combined with chemotherapeutic agents (Benkovic et al. 2007).

The ability of health scientists to measure the activity of honey in cancer is related to factors within a matrix of diverse botanical, entomological and geographical origin (major sugar components, water, polyphenols and other secondary plant metabolites, acids, enzymes, minerals, etc.), cancer type (adenoma, carcinoma, myeloma), organ site, cancer stage (initiation, metastasis, double tumor), cancer care (mucositis, radiation burns), patient age, and presence of other diseases. Cascades of molecular markers as indicators of cancer onset and anticancer action are actively investigated. Whether honey is useful to treat cancer is a question to be answered in relief of oncologic suffering and death.

This study aims to provide an overview in the usefulness of honey in cancer prevention and therapy. Our data on the antiproliferative action of pot-honey from *Frieseomelitta*, *Melipona*, *Scaptotrigona*, and *Tetragonula* in three human ovarian cancer cell lines are described and evaluated here.

35.2 Cancer

The name “cancer” originated with Hippocrates and the Greek word ‘carcinos’ “καρκίνος” to indicate tumors with the shape of a crab. All cancer cells in a patient originate from a unique cell starter among the 10^{14} cells in the human body (Pecorino

2008) as the primordium of this progressive disease. One initial mutation accumulates in a single cell, causes unregulated cell growth, invasion of surrounding tissues, and eventually spreads. The disease is therefore clonal, and may evolve more than 10 years before clinical detection. The multistep process leading to the development of cancer is known as carcinogenesis. Proto-oncogenes are activated, while tumor suppressor and genomic stability genes are inactivated. A colon cancer model gave seminal evidence for cancer genetic and histological multistage progression (Volgestein et al. 1988). Age is the biggest risk factor for cancer (Tovey et al. 2007).

The following six cell-markers differentiate cancer cell behavior from normal cells: (1) Evasion of apoptosis. (2) Growth signal autonomy, (3) Evasion of growth inhibitory signals, (4) Angiogenesis, (5) Unlimited replicative potential, and (6) Invasion and metastasis (Hanahan and Weinberg 2000). Molecular pathways and signaling used in cell function are considered to understand how a normal cell transforms into a cancer cell, and also how cancer cells alter tissue, organ and body functions. Any group of cells out of place is considered cancer in medical imaging. A new growth of cells is called a "neoplasm". Oncology is the medical discipline specialized in cancer, and is also originated from a Greek word "onkos" "ογκος", which means bulky mass.

Carcinomas are the most common tumors and occur in epithelial cells (e.g., brain, colon, kidney, lung, skin, stomach); sarcomas develop in mesoderm cells (e.g., bone, muscle), and adenocarcinomas develop in glandular tissue (e.g., breast, prostate, pancreas). The situation becomes more complex when examining molecular mechanisms, target tissues and cell types, patterns of metastasis, and causes. Besides the ability of cancer to invade other organs during final stages, secondary effects of cancer treatment also cause pain. Cancer patients tend to have wounds that fail to heal (Mc Nees and Dow Meneses 2007), causing suffering and death. Radiation-induced oral mucositis, stomatitis, malignant ulcers, infected lesions, and an infected oral cavity in head and neck cancer are common (Bardy et al. 2008). The feeling of helplessness is often the main cause of increasing pain in cancer (Toon 2008).

Official labeling of a cancer drug contains approved information for the product. It covers a number of categories for precise use in terms of type and subtype of cancer, dose, association, schedule and route of administration, and duration of treatment according to the course of the disease. In medical practice, use outside this frame is considered "off-label" prescription (Levêque 2008) but does not apply to traditional use of phytochemicals, including honey.

35.3 Multidrug Resistance Caused by Chemotherapy

Cells repeatedly exposed to anticancer drugs may develop drug resistance due to intrinsic or extrinsic factors of diverse nature. Tumor cells exposed to toxic agents increase their tolerance to drugs by adaptive response. Several molecular mechanisms that cause multidrug resistance have been described. First, there may be a reduced drug uptake and increased drug efflux at the membrane level. Second, enhanced drug

detoxification in cytoplasmic thiol systems, through glutathione S-transferases may occur. Third, there may be increased DNA repair by enzymes. Additionally, decreased apoptosis has three metabolic pathways; (1) overexpression of anti-apoptotic proteins, (2) underexpression of pro-apoptotic proteins, and (3) altered subcellular distribution of wild type p53 protein, called the "guardian of the genome". Studies on sequenced combination of cisplatin and other platinum compounds with phytochemicals are being carried out in the cancer research laboratory at the Discipline of the Biomedical Science at The University of Sydney (F. Huq 2011, personal communication) with the aim of surmounting cisplatin resistance in ovarian cancer.

35.4 Honey and Cancer

Because honey may be viewed as a medicinal dietary substance, scientific evidence on the benefits of honey have been growing since the ancient claims about health and longevity, e.g., by Hippocrates (Skiadas and Lascaratos 2001). Markers of human health suggest that honey consumption reduces the risk of diseases causing death (Cooper et al. 2010). The immunological activity mediated by cytokines is an important functional property modulated by honey (Tonks et al. 2001, 2003, 2007). Healing properties of bee products are related to the antioxidant, anti-inflammatory, antimicrobial, and anticancer activities of flavonoids. However, other substances such as amino acids, vitamins and organic acids can also contribute to the healing power of honey (Frankel et al. 1998) and its useful inclusion in the diet to complement other polyphenols (Blasa et al. 2006). One study indicated the presence of a tumor-promoting factor in honey (Upadhyay et al. 1980), but in current research honey is found to be healing. The antitumor activity of honey may occur through the activation of macrophages, T- and B-cells (Attia et al. 2008). The antiproliferative effect of honey in colon cancer cells is found to vary depending on honey's botanical and geographical origin (Jaganathan and Mandal 2009b). Although Indian honey has been applied in culture media (Jaganathan et al. 2010), most studies use phenolic extracts of honey. Methanol extracts of Malaysian honey showed a higher phenolic content, whereas an ethyl acetate extract was more active to reverse the toxicity caused by tumor necrosis factor (Kassim et al. 2010).

In research with human cancer cell lines, antiproliferative action of honey was observed by apoptosis with IC_{50} values (the concentration at which cell proliferation is inhibited by 50%) of 4, 10, and 14% after 24, 48, and 72 h, respectively, in a prostate PC-3 cell line (Samarghandian et al. 2010), and with an IC_{50} of 1.7 and 2.1 μg/mL after 48 and 72 h in renal cell carcinoma (Samarghandian et al. 2011). Therefore, the apoptotic nature of honey has potential for the treatment of prostate and kidney cancer. Honey of the giant honey bee *Apis dorsata*, reportedly from nesting in the large forest tree "Tualang" (*Koompassia excelsa*, Fabaceae) in Malaysia was found to induce apoptosis in human oral squamous cell carcinomas, osteosarcoma (Ghashm et al. 2010), and breast and cervical cancer cell lines by depolarization of the mitochondrial membrane (Fauzi et al.).

Evidence of medicinal uses of honey in oncological care is found in reviews in the Journal of Clinical Nursing (Bardy et al. 2008; Gethin 2008). Nurses are directly involved in healthcare intervention, and have extensive contact with patients. They have often encountered secondary effects caused by conventional treatments of neoplasias. Honey is used to prevent neutropenia (Zidan et al. 2006), in pediatric hematology–oncology wound care (Wiszniewsky et al. 2006), for radiation induced skin toxicity (Moolenaar et al. 2006), mucositis (Motallebnejad et al. 2008), and as a potent antibacterial agent in cancer patients (Majtan et al. 2011).

35.4.1 The Botanical Diversity of Honey

Plants visited by bees have been of great interest to diverse disciplines, and melissopalynology provides a tool to study the pollen residues of honey as a "fingerprint" potentially indicating botanical origin of nectar (but see Chap. 21, Roubik and Moreno in this book). Honey with more than 45% pollen counts of one taxon is considered unifloral (Louveaux et al. 1978). The honey of chestnut (*Castanea sativa*) has been studied for aroma composition (Castro-Vázquez et al. 2010), and manuka (*Leptospermum*) honey for its medicinal properties (Molan 2001; Tonks et al. 2007). Different plants may well confer different properties to honey. Sensory and physicochemical patterns described for 13 unifloral European honeys produced by *Apis mellifera* (Persano Oddo and Piro 2004) were further investigated for their aroma composition and medicinal properties. As an example, the antimutagenic activity of honey from seven different floral sources: acacia (*Robinia pseudoacacia*), buckwheat (*Fagopyrum esculentum*), clover (*Melilotus*), fireweed (*Epilobium angustifolium*), soybean (*Glycine max*), tupelo (*Nyssa*), and Christmas berry (*Schinus terebinthifolius*), and the sugars glucose, fructose, maltose, and sucrose, was measured against nonpolar heterocyclic amine Trp-p-1 (3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole) and tested via Ames assay (Wang et al. 2002). Sucrose was not active, but fructose and glucose were more antimutagenic than honey and the weak maltose, against Trp-p-1. Buckwheat honey, which is extremely high in phenolics caused the greatest inhibition (52.1%) at 1 mg/mL, indicating its potential for use in anticancer therapy.

35.4.2 How Many Kinds of Bees Produce Honey?

There are approximately 750 bee species that make honey, about 250 of which are in the genus *Bombus*, and not considered here (Michener 2007). Hymenoptera are one of the largest and most biologically diverse orders of phytophagous insects with various social grades, and a range of parasitic species (La Salle and Gauld 1993). Phylogenetic relationships of the hymenopteran superfamily, to which all types of bees belong, were initially resolved by sequenced mytochondrial genomes as a single

analytical approach (Dowton et al. 2009). However, mtDNA is not conservative enough to have any resolution power earlier than the Pliocene, needed to study bee phylogenies, as reviewed by Roubik 2012.

In nature, honey is derived from water–sugar resources available in the environment, processed and accumulated for energy needs of the bee colony. Honey bees (*Apis* spp., Apini) store their honey in beeswax combs, while stingless bees (Meliponini) use cerumen pots of different sizes, shapes, and colors. Apini has 11 or 12 species in the single genus *Apis*, but Meliponini has more than 500 species in approximateley 61 genera (Rasmussen and Cameron 2010; Roubik 2012). The great biodiversity of Meliponini is treated in the contributions by Camargo and by Michener (Chaps. 1 and 2), in this book. Honey produced by Meliponini clustered naturally according to entomological origin, using compositional data (Vit et al. 1998). Therefore, the entomological origin of honey adds an important descriptor to any medicinal application of honey.

35.4.3 Flavonoids as Anticancer Components of Honey

Cancer chemoprevention is an important issue concerning dietary components such as polyphenols, and their epigenetic role as modulating agents of gene expression (Jaganathan and Mandal 2009a; Link et al. 2010; Szic et al. 2010). Thus, flavonoids in honey have been studied for their chemopreventive action. Chemopreventive properties of dietary polyphenols (catechin, chrysin, epicatechin, epigallocatechin-3-gallate, quercetin, rutin, myricetin, resveratrol, and xanthohumol) are associated with multiple molecular mechanisms of action against colorectal cancer cell lines (Araújo et al. 2011). Phytochemicals are also studied as agents that may help to counter multidrug resistance in combined treatments (Yunos et al. 2010). An hypothesis on the genotoxic role of honey flavonoids targeting cancer cells has been proposed (Jaganathan 2011).

Flavonoids are a group of small molecules (C6-C3-C6, MW ~ 300) widely known to contribute to the colors of flowers and fruits. Five subclasses of dietary flavonoids were considered in selected food: flavones, flavonols, flavanones, flavan-3-ols, and anthocyanidins (USDA 2007). In this database there is an entry for a content of reference flavonoids in 100 g honey: 0.05 mg apigenin, 0.63 mg luteolin (flavones) and 0.17 mg isorhamnetin, 0.11 mg kaempferol, 1.03 mg myricetin, 0.51 g quercetin (flavonols). Over the past few years, a number of studies have used flavonoid profiles of honey to find botanical and other markers, such as bee species (Vit and Tomás-Barberán 1998), and locations of origin (Tomás-Barberán et al. 2001).

The removal of free radicals—named scavenging, is one of the outstanding medicinal attributes of flavonoids (Havsteen 2002). Phosphorylation and dephosphorylation reactions that regulate the Na^+/K^+ ion pump are sensitive to flavonoids. Quercetin removes the phosphate ester from the phenol group tyrosine and restores the pH value in cancer cells (Spector et al. 1980). Apigenin and luteolin are potent inhibitors in human thyroid carcinoma cell lines (Yin et al. 1999). Polyphenols

studied to characterize and differentiate bee products are a valuable background for predictions on what honey types may have anticancer value.

The antiproliferative effects of honey are mainly explained by the presence of the flavonoid chrysin (5,7-dihydroxyflavone). Flow cytometry analysis indicated that cytotoxicity induced by honey or chrysin was mediated by G(0)/G(1) cell cycle arrest. Chrysin was therefore considered a potential candidate for both cancer prevention and treatment (Pichichero et al. 2010). Chrysin has been widely studied by several authors for its effect in suppressing inflammation caused by NF-κB and JNK activations (Ha et al. 2010), to trigger the unfolded endoplasmic reticulum resident protein GRP78 response (Sun et al. 2010), to enhance the apoptosis induced by a ligand (Li et al. 2011), p38 and Bax activation (Pichichero et al. 2011). However, in another study, chrysin inhibited the apoptosis induced by the antitumor-drug topotecan by inhibiting ATP-binding cassette (ABC) transporters (Schumacher et al. 2010).

35.5 Is Pot-Honey Cytotoxic to Human Ovarian Cancer Cells?

Substances such as antioxidants that can be chemopreventive to normal cells can also be cytotoxic to cancer cells. Often, these opposing properties are manifested in different cell receptors. It is possible that honey can play both chemopreventive and cytotoxic roles, perhaps due to a variety of antioxidants. To answer this question, the survival of human ovarian cancer cells was measured in the presence of 200 mg honey/mL and three lower serial dilutions up to 1.6 mg honey/mL. The MTT reduction assay (Mosmann 1983) was carried out to determine cell kill due to 16 pot-honey samples produced by 13 species of stingless bees (eight *Melipona* species, three *Scaptotrigona* species, *Tetragonula carbonaria*, and *Frieseomelitta nigra* obtained from Australia, Brazil, Mexico, or Venezuela).

The IC_{50} values of honey samples against three human ovarian cancer cell lines (i.e., concentrations of honey required for 50% cell kill) are given in Table 35.1. The results show that honey samples vary widely in their ability to cause cell kill. The most active honey sample against parent A2780 cell line is *Melipona solani* (2.74 mg/mL) and the least active one is *Melipona scutellaris* (24.37 mg/mL). The next two more active honey samples are *Melipona favosa* (3.39 mg/mL) and *Scaptotrigona polysticta* (3.60 mg/mL), followed by *Scaptotrigona hellwegeri* (4.19 mg/mL), *Melipona beecheii* (4.24 mg/mL), and *Frieseomelitta nigra* (4.58 mg/mL). The activity of cisplatin is found to be much lower in the resistant $A2780^{cisR}$ (3.88 μM) and $A2780^{ZD0473R}$ (3.44 μM) cell lines, as compared to that in the parent A2780 cell line (0.88 μM). Unlike that of cisplatin, generally the activity of the honey samples in the resistant cell lines is found to be comparable to that in the parent cell line or greater except in the case of *Melipona subnitida* (as applied to $A2780^{ZD0473R}$) where the activity is some 50% lower in the resistant cell lines. Greater activities of some honey samples, especially *Melipona solani* (1.66 and 0.79 mg/mL) and *Scaptotrigona polysticta* (1.54 and 1.36 mg/mL) in the resistant $A2780^{cisR}$ and $A2780^{ZD0473R}$ cell

Table 35.1 IC_{50} values of pot-honeys in the human ovarian cancer cell lines

		Ovarian cancer cell lines				
		A2780	$A2780^{CisR}$		$A2780^{ZD0473R}$	
		IC_{50}	IC_{50}	RF	IC_{50}	RF
Geographical origin, city, country	Cisplatin (control)	0.88	3.88	4.42	3.44	3.91
	Pot-honey bee species					
Chetumal, Mexico	*Melipona beecheii*	4.24	3.35	0.79	4.14	0.98
El Reventón, Mexico	*Melipona fasciata*	6.17	4.72	0.77	4.28	0.69
Moura, Brazil	*Melipona fasciculata*	6.18	5.83	0.94	5.89	0.95
Tabocas, Brazil	*Melipona fasciculata*	8.00	3.97	0.50	5.15	0.64
Preazinho, Brazil	*Melipona fasciculata*	13.56	6.69	0.49	7.69	0.57
Moruy, Venezuela	*Melipona favosa*	16.50	4.21	**0.26**	12.81	0.78
Moruy, Venezuela	*Melipona favosa*	3.39	3.68	1.08	3.65	1.08
Belém, Brazil	*Melipona rufiventris*	5.10	4.68	0.92	3.80	0.74
João Pessoa, Brazil	*Melipona scutellaris*	**24.37**	**25.72**	1.06	**27.64**	1.31
Chiapas, Mexico	*Melipona solani*	**2.74**	1.66	0.61	**0.79**	**0.29**
Natal, Brazil	*Melipona subnitida*	17.54	27.60	**1.57**	34.36	**1.96**
El Reventón, Mexico	*Scaptotrigona hellwegeri*	4.19	4.59	1.10	4.10	0.98
Cuetzalan, Mexico	*Scaptotrigona mexicana*	7.71	4.43	0.57	5.62	0.73
Xingú, Brazil	*Scaptotrigona polysticta*	3.60	**1.54**	0.43	1.36	0.38
Brisbane, Australia	*Tetragonula carbonaria*	8.96	4.76	0.53	4.54	0.51
Guerrero, Mexico	*Frieseomelitta nigra*	4.58	4.72	1.03	4.19	0.92

IC_{50} honey (mg/mL), cisplatin (μM), *RF* resistance factor as the ratio IC_{50} resistant cell line/IC_{50} parent cell line

lines, respectively, than in the parent A2780 cell line, indicate that the pot-honey samples have been able to overcome (at least partially) cisplatin resistance operating in the cell lines. The lowest resistance factor in this set of experiments was achieved by honeys of *Melipona favosa* against $A2780^{cisR}$ (0.26) and *Melipona solani* against $A2780^{ZD0473R}$ (0.29). Further studies would be required to obtain information about the mechanisms of cell killing effect by the pot-honeys, and what active components confer their antiproliferative activity.

The second honey of *Melipona favosa* (V12 in APIBA honey collection), was 4.5× richer in flavone *C*-glycosides than V9, and half in flavonol *O*-glycosides (Truchado et al. 2011). More precisely, enzymatic hydrolysis of flavone *C*-glycosides could produce cytotoxic metabolites, or a *C*-glycoside fit in a signaling molecular pocket to explain the observed higher cell kill.

Much needed experiments should compare honey of the same species of bee fed from different kinds of flowers, and of different species of bees fed on the same species of flower. With bee colonies in greenhouses, so that the flowers available to them would be clearly known, such experiments would be possible. With such experiments, the sources of anticancer compounds, whether from flowers or bees or both, could be determined. The very different numbers sometimes shown in Table 35.1 for the same species of bees may suggest the great influence of the floral resources.

35.6 Adaptive Response of Cancer and Normal Cells to Honey

This review to approach the anticancer action of honey involved studies of a variety of mechanisms. We have highlighted three main issues. First, the complexity of the problem from both sides of honey and cancer biodiversity is discussed. Second, the role of honey in chemoprevention is shown. The action of some active components such as flavonoids and the well-known nature of high sugar concentration are discussed. Third, the therapy after cancer onset, with combined treatments using conventional chemotherapy and alternative medicine, is considered. Finally, the effect of pot-honey in a model based on human ovarian cancer cell lines was compared between the stingless bee genera *Frieseomelitta*, *Melipona*, *Scaptotrigona*, and *Tetragonula*.

The adaptive response of cancer and normal cells to honey is a mosaic under construction, and we hope that it will lead to a model for a better understanding of flavonoid interactions with cells, as a chemopreventive and genotoxic tool. Generations of anticancer agents with reduced toxicity in cancer patients may have honey as an ingredient of preparations with other natural products such as *Aloes*, or combined with targeted therapy.

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