7. Systematic reviews on interventions with honey in cancer

VIT Patricia[1,2]*, HUQ Fazlul[2]

[1]Apitherapy and Bioactivity, Food Science Department, Faculty of Pharmacy and Bioanalysis, Universidad de Los Andes, Mérida 5101, Venezuela.

[2]Cancer Research Group, Discipline of Biomedical Science, Cumberland Campus C42, The University of Sydney, 75 East Street, Lidcombe NSW 1825, Australia.

* Corresponding author: Patricia Vit, Email: vitolivier@gmail.com

Received: September 2012; Accepted: January, 2013

Abstract

Interventions with honey in cancer were systematically reviewed based on three databases (AMED, CINHAL, MEDLINE), as a mandatory tool for evidence-based medicine. The information was categorized using hand search (number of articles in brackets) into three sets: 1. Supportive care for human cancer (4). 2. Therapeutical uses of honey in cancer models *in vivo* (3). 3. Experimental uses of honey and flavonoids in cultured cancer cells (7). Honey type, dosage, time sequence, organ with cancer, patients, intervention, conclusions, follow-up, authors and countries are presented for each study.

Keywords:
cancer, databases, honey, systematic reviews

Introduction

The Bible, the Torah, the Qu'ran and ancient pharmacopeias mention honey as a remedy to cure mankind (Jones, 2009), even from cancer (Gribel and Pashinkii, 1990), which is more successful during early phases of the disease (Cantor, 2008).

Information on the properties of honey is needed for sensible choices in healthcare (Gethin, 2008). Medical grade honey is achieved by special processing to meet quality standards (Yoon and Newlands, 2005; Acton and Dunwoody, 2008). Manuka (*Leptospermum* spp. Myrtaceae) honey is leading this application, needed to develop the industry of pot-honey. Wound management with honey dressings is effective (Sharp, 2009; Descottes, 2009). However, perceptions of safety of honey in traditional and complementary medicinal approaches vary among diverse ethnic populations (Kumar et al., 2011). Cancer prevention and therapy using honey alone or honey combined with plants or chemotherapy have been recently reviewed (Vit et al., 2012). In this work we systematically reviewed current literature to mine information on interventions with honey in humans, *in vivo* models and cultured cancer cells.

7.1 Systematic reviews for clinical and experimental interventions with honey

Systematic reviews (SR) are a mandatory tool for evidence-based medicine. Updating needs to be frequent if the search is sought to be relevant to clinical practice and the delivery of health care (Shojania et al., 2007). Further contact with the oral mucositis (methods, participants, interventions, outcome measures, results and risk of bias) was used to accomplish unambiguous details (Worthington et al., 2010).

A search strategy was discussed and performed with the Faculty of Health Science Liason Librarian Ms Elaine Tam. Besides honey, a set of six search terms consisting of cancer, carcinoma, metastasis, neoplasm, oncology and tumor, were used as keywords for the search.

The six groups that were generated were linked to each other with "or". Cancer related exploded set of references "and" honey exploded set of references were searched in the following databases: AMED (1985 to present), CINAHL (1982 to August 2012), MEDLINE (1948 to August 2012). Inclusion (comparative studies, written in English) and exclusion (abstracts, other languages) criteria were used to screen all references.

A set of AMED (4), CINHAL (26) and MEDLINE (50 articles) were retrieved. Subsequently, a hand search was done to categorize the search results in three groups: 1. Supportive honey care for human cancer (See Table 1). 2. Therapeutical uses of honey in cancer models *in vivo* (See Table 2). 3. Experimental uses of honey and flavonoids in cultured cancer cells (See Table 3). Honey is being used for wound management (in advanced cancer stages, after surgery, chemotherapy and radiation), as chemotherapeutic agent, and to decrease cancer implantation.

Table 1. Supportive honey care for human cancer

Honey type	Honey dosage and time sequence	Organ	Patients, intervention	Conclusion	Follow up	Author , year (country)
tea plant *Camelia sinensis*	20 mL honey 15 min before, 15 min and 6 h post-radiation therapy	head neck	Forty patients, radiation induced mucositis	Topical application of honey is a simple and cost-effective treatment in radiation mucositis	Further multi-centre randomized trials to validate our finding	Biswal et al., 2003 (Malaysia)
manuka (*Leptospermum* spp.)	review on wound care	skin	Four patients, dehiscent thoracotomy wound after resection of pulmonary metastases, primary tumor, superficial wound after chemotherapy with autologus stem cell transplantation, drainage wound after splenectomy	promising experience	Internet-based standardized documentation system for wound healing in children successfully managed with Medihoney	Simon et al., 2006 (Germany)
-	review on oral mucositis	-	-	-	Need for further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent	Worthington et al., 2010 (UK)
manuka (*Leptospermum* spp.)	honey-coated bandages 4 week	breast, head, neck	Thirty-seven patients with malignant wounds of advanced stage cancer	62% of patients reduced wound size, 58% improved wound cleanliness, reduced malodour and exudation	The use of honey bandages improved the quality of life, reduction of wound size increased survival of patients	Lund-Nielsen et al., 2011 (Denmark)

Honey type, dosage and sequence of addition are given except in the review articles. Common wound care situations of four patients in pediatric oncology included dehiscence and infection after tumor biopsy or surgery, ulcers due to tumor cachexia or induced by chemotherapy, and skin necrosis due to extravasation of cytotoxic drugs, besides infections in another group (Simon et al., 2006).

Systematic reviews (SR) on the uses of honey within the oncological care come from nursing (Bardy et al., 2008; Gethin, 2008), subsequent to their exhaustive and recurrent contact with secondary effects caused by conventional treatments of neoplasias. Nurses are directly involved in healthcare interventions and have large contact with patients. 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 potent antibacterial agents in cancer patients (Majtan et al., 2011).

Honey was successfully included among nine clinical interventions, with more than one trial in the meta-analysis, and statistically significant evidence was found for either preventing or reducing the severity of oral mucositis after cancer therapy, compared to either a placebo or no treatment. In a review of 131 studies, *Aloe vera* and honey showed evidence of a benefit to prevent or to reduce the mucositis, varying with the type of cancer and treatment (Worthington et al., 2010). In a previous Russian study with murine tumors, honey alone showed moderate antitumor activity and pronounced antimetastatic effects. Honey combined with the anticancer drugs 5-fluorouracil and cyclophosphamide, potentiated the antitumor activity (Gribel and Pashinkii, 1990). Implications for practice include consideration that benefits may be specific for certain cancer types and treatment (See Table 2). The antiproliferative and modulatory apoptitic action of honey and flavonoids is also studied in cancer cells (See Table 3).

Table 2. Therapeutical uses of honey in cancer models *in vivo*

Honey type	Honey dosage and time sequence	Organ	Tumor type (animal)	Conclusion	Follow up	Author, year (country)
-	10, 100, 1000 mg/ 100 g BW every other day for 4 weeks before intraperitoneal inoculation EAT	peritoneum	Ehrlich ascites tumor EAT (mice)	The antitumor activity of honey may occur through the activation of macrophages, T-cells and B-cells.	-	Attia et al., 2008 (Egypt)
-	review	-	-	Honey was suitable alternative for wound healing, burns and various skin conditions and a potential role within cancer care	Induced mucositis, radiotherapy-induced skin reactions, hand and foot skin reactions in chemotherapy patients and for oral cavity and external surgical wounds	Bardy et al., 2008 (UK)
-	wounds coated with honey before and after tumor inoculation	posterior neck	Ehrlich ascites tumor (BALB/c mice strain)	Tumor implantation decreased with honey application	Honey could be used as a wound barrier against TI during pneumoperitoneum in laparoscopic oncological surgery and in other fields of oncological surgery	Hamzaoglu et al., 2000 (Turkey)

Table 3. Experimental uses of honey and flavonoids in cancer culture cells

Honey type or flavonoid	Honey or flavonoid dosage and time sequence	Honey or flavonoid IC_{50} (%)	Organ	Cell lines	Conclusion	Follow up	Author, year (country)
Multifloral from the Malysian forest known as Tualang honey	(1–10%) for up to 72 h	2.4-2.8	breast womb	human breast cancer MCF-7 MDA-MB-231 normal breast epithelial MCF-10A cervical HeLa	-	-	Fauzi et al., 2011 (Malaysia)
Multifloral Malaysian ***Apis dorsata*** nests on *Koompassia excelsa* "tualang" tree	1% - 20% 3, 6, 12, 24, 48 and 72 hours	OSCC 4.0% HOS 3.5% max inhibition cell growth at 15% honey	oral cavity jaw bones	human oral squamous cell carcinomas (OSCC) osteosarcoma (HOS)	Time and dose-dependent antiproliferative effect by inducing early apoptosis	to determine the molecular mechanism of apoptosis	Ghashm et al., 2010 (Malaysia)
-	review	-	-	-	-	clinical trials are needed to validate honey applications	Jaganathan and Mandal, 2009 (India)
Indian ***Apis cerana*** Eastern Himalaya West Bengal State	-	-	colon	human colon cancer HCT-15 and HT-29	Accumulation of the sub-G(1) phase of cell cycle indicating apoptosis, depletion of intracellular non protein thiols, reducing the mitochondrial membrane potential (MMP) and increasing the reactive oxygen species (ROS) generation, up-regulating the p53 and modulating the expression of pro and anti-apoptotic proteins. Further apoptosis induction was substantiated using DNA fragmentation assay	Promote honey as a potential chemo-therapeutic agent against colon cancer	Jaganathan et al., 2010a (India)
Indian A Kashmir West Bengal Uttar Pradesh and eugenol	-	22.40 – 33.50 7.33 – 8.47 mg/mL	breast	MCF-7	Rich polyphenolic profile inhibited induced oxidative cell death, dose-dependent inhibition, apoptotic action	Promoting honey as a potential candidate for breast cancer treatment	Jaganathan et al., 2010b (India, USA)
Gelam (*Melaleuca* sp.) honey methanol extract (HME) ethyl acetate extract (HEAE)	-	235.4 µg/mL HME 168.1 µg/mL HEAE	-	murine fibrosarcoma cell line L929	Tumor necrosis factor-(TNF-α) cytotoxicity	-	Kassim et al., 2010 (Malaysia)
Tetragonula laeviceps water (WEH)	-	-	breast	BT474	Water extract of honey provided better antiproliferative action		Chanchao, 2012 (Thailand)

7.2 Wound management

Dressing wounds with raw honey was a traditional practice in ancient cultures (Zumla and Lulat, 1989), until the discovery and expansion of antibiotics in the pharmaceutical industry (Forrest, 1982). Along time, microbes developed antibiotic-resistance and the therapeutic use of natural products such as honey was revisited (Molan, 1999). Medical grade wound honey care creams, gels, impregnated gauzes and dressings to treat wounds are now available to the public (Bogdanov, 2012). They have been registered by medical regulatory authorities in Australia, Canada, the European Union, Hong Kong, New Zealand and the USA (Irish et al., 2011).

Five mechanisms of action are identified for the honey interventions: 1. antibacterial power, 2. anti-inflammatory effect, 3. debridment of sloughy and necrotic tissues, 4. moist milieu of the wound, aiding autolytical debridment (Robson, 2002), and 5. reduction of malodor (White, 2005; Cutting, 2007). Physicochemical properties of honey do so: 1. High viscosity creates a protective layer between wound bed and dressing, 2. high osmolarity extracts fluid from underlying tissues, 3. low pH inhibits bacterial growth, 4. deodorization of offensive smelling is achieved by microbial metabolic preference of sugars leading to lactic acid instead of putrid protein byproducts, 5. polyphenols and other non-peroxide bioactive phytochemicals (not degraded by catalase like hydrogen peroxide) reduce inflammatory signaling (Molan and Russell, 2008), 6. enzymatic production of hydrogen peroxide exerts antimicrobial effect (White et al., 1963; Bang et al., 2003), 7. a cationic antimicrobial peptide bee defensin-1 (Kwakman et al., 2010), 8. antioxidant-pro-oxidant systems of honey protect tissues from oxidative stress and attack harmful microbes, 9. the water content has been explained for maturation of honey in combs but it is also a mean for fermentive processes of pot-honey –more studies are needed; additionally, 10. due to its hydrocolloidal nature, honey water soluble components act as a serum, stimulating the synthesis of collagen and reducing the formation of scar tissue (Molan, 1999). The paradox here is that being honey a nutritive matrix for microbial growth, it also has elements to control/prevent microbial growth.

A multilayer adsorbed honey film on tin surface was attributed to inhibit tin corrosion of honey alone or combined with black radish juice, in contrast with the mechanism of inorganic elements acting as anodic inhibitors to increase corrosion resistance (Radojcic et al., 2008)

Diverse types of wounds such as chronic ulcers, burns, diabetic foot, gangrene, oncological wounds caused by surgical removal of tumors, radiotherapy, and mucositis after chemotherapy, are successfully treated with honey. The exudative and resorptive phases –also known as ‘cleansing’, are extended in chronic wounds that cannot reach maturation towards proliferative and regenerative phases of healing (Zerm, 2012). They have a recurrent breakdown because non viable tissue is avascular, therefore it has pale-greyish color and slow granulation, and does not reduce size or even increases size over time. This external appearance is explained by molecular, biochemical and cellular imbalances, including elevated inflammatory cytokines, elevated matrix metalloproteinases (MMPs) and decreased tissue inhibitors of metalloproteinases (TIMPs), causing low mitotic activity, senescence and decreased growth factor activity (Templeton, 2005). Wound environment is managed by: T Tissue management, I Inflammation and infection control, M Moisture balance, E Epithelial progress in the edge of the wound. This gives the acronym TIME.

Honey concentrations between 30-50% could control urinary tract infections better than cephaloridine, ampicillin, gentamycin among others (Ibrahim, 1981). Also lower concentrations of honey (5 to 20%) inhibit pathogenic bacterial growth (Lusby et al., 2005). At a lower concentration (0.1%) honey can boost the immune system by stimulating the proliferation of lymphocytes in cell culture and activating phagocytes from blood (Abuharfeil et al., 1999), but at 1% honey stimulates monocytes to release cytokines and initiate the cascade of immune response causing infection (Tonks et al., 2001). A honey concentration switch may be considered to explain these contrasting effects.

Different nectars provide unique antibacterial factors to honey, causing different mechanisms of antibacterial activity (Chang et al., 2011; Kwakman et al., 2011; Liberato et al., 2011). Excisional wound healing was achieved with Tualang honey from Malysia (Tan et al., 2012). Only some types of honey are beneficial in wound care (Acton and Dunwoody, 2008). However, the sugars in honey may explain some 50% of its antibacterial activity (Kwakman et al., 2011).

White’s (2005) perspective and admiration of honey as a bioactive dressing: “within a single product a range of actions usually available only individually in a range of products”, as illustrated in the surah on the bees from the Qu'ran 16:68-69: “And your Lord inspired the Bee, saying: ‘Take your

habitations in the mountains and the trees and in what they erect. Then eat of all fruits, and follow the ways of your Lord, made easy (for you).' There comes forth from their bellies a drink of varying colour wherein is a healing for men. Verily, in this is indeed a sign for people who think."

7.3 Antiproliferative action of honey in cancer cultured cells

How honey kills bacteria and does not kill the cells in wound tissue is in the same line of thought on why honey kills cancer cells but not surrounding healthy tissue. Competition for nutrients between tissue cells and pathogens in chronic infected wounds is also true between healthy and tumoral cells. The function of dietary nutrients *in vivo* may result in anticancer effects. Each nutrient may become an active principle or act in concert with other components or conventional therapies. The apoptotic nature of honey is relevant to its antiproliferative action because most anticancer drugs are apoptotic inducers. Honey dilutions, water and organic extracts or honey components are valid approaches to investigate the antiproliferative role of honey in cancer cultured cells. An extensive review of polyphenols from honey acting as antiproliferative agents is provided by Jaganathan and Mandal (2009).

Interactions with membrane, intracellular receptors, and nitric oxide synthase inhibition were suggested as possible mechanisms to explain antiproliferative and apoptotic effects of phenolic acids in T47D human breast cancer cells (Kampal et al., 2004). Synergistic effect of quercetin and kaempferol in reducing cell proliferation at 4 and 14-days single exposure in the human gut (HuTu-80, Caco-2) and breast cancer cells (PMC42) were associated with decreased expression of nuclear proliferation antigen Ki67 and total protein levels in treated cells relative to controls (Ackland et al., 2005).

Phenolics in honey are bound to sugar moieties, and become more water soluble (D'Arcy, 2005). Their antioxidant activity has a role in preventing free radical damage known to happen in cancer. Phenolics can be specific free radical scavengers to block tumor necrosis factor (TNF-α) mediated cytotoxicity. Hesperetin and naringin can inhibit nitric oxide (NO) production induced by lipoxigenase (LPS). Quercetin, caffeic acid, chrysin and ellagic acid down-regulate the nuclear factor-κB (Romier et al., 2008), reducing the biosynthesis of iNOS and consequently of NO. 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).

The antiproliferative, apoptotic, and antitumoral activities showed IC_{50} values of 1.7% and 2.1 % after 48 h and 72 h exposure to multifloral honey from Iran in renal cancer cell lines ACHN (Samarghandian et al., 2011). Tualang honey *Koompassia excelsa* produced by Malaysian *Apis dorsata* induced time and dose-dependent antiproliferative effect by early apoptosis with the following IC_{50} values in human oral squamous cell carcinomas OSCC (4%) and osteosarcoma HOS (3.5%) (Ghashm et al., 2010). IC_{50} values of gelam honey (*Melaleuca* sp.) from Malaysia towards HepG2 (cancer liver) and WRL-68 (normal liver) cells were 25% and 70% respectively (Jubri et al., 2012). Water extracts of the stingless bee *Tetragonula laeviceps* pot-honey from Thailand provided better antiproliferative action in breast cancer cells BT474 than ethanol extracts (Chanchao, 2012), IC_{50} values of crude extracts with hexane (3.41%) dichloromethane (5.70%). No difference was observed between water and ethanol extracts in liver cancer cells HepG2, and low IC_{50} were found for crude extracts with hexane (2.44%) dichloromethane (4.21%).

7.4 Apoptotic hallmarks of honey

Apoptosis prevents cancer cell proliferation by programmed cell death in healthy tissues. Therefore, compounds preserving or activating apoptosis are chemopreventive. Loss of apoptosis and inflammation onset –mediated by cytokines, nitric oxide, prostaglandins– occur in cancer.

The proapoptotic changes, indicating antitumor activity against oral carcinoma and osteosarcoma, increased at higher concentrations of Tualang *Apis dorsata* honey. Early apoptotic dead cells became rounded, with blebbed membrane, nuclear shrinkage, chromatin condensation and fragmented nucleus on OSCC and HOS cell lines (Ghashm et al., 2010).

Indian *Apis cerana* honey promoted apoptosis of human colon cancer cells HCT-15 and HT-29 via cell cycle arrest at sub-G1 phase, activation of p53 and caspase-3 caused depletion of intracellular non protein thiols, reduced the mitochondrial membrane potential (MMP) and increased the reactive oxygen species (ROS) generation (Jaganathan et al., 2010a).

Tualang (multifloral *Apis dorsata* from the forest) honey from Malaysia induced apoptosis of breast and cervical cancer cells (Fauzi et al., 2011). Gelam (*Apis mellifera*, *Melaleuca* sp. Myrtaceae) and Nenas (*Apis mellifera*, *Ananas comosus* Bromeliaceae) Malaysian

honeys inhibited the proliferation of HT29 colon cancer cells by inducing DNA damage, early and late apoptosis, and reduced inflammation (Wen et al., 2012).

Some bioactive phytochemicals in honey are proapoptotic. Eugenol inhibited induced dose-dependent oxidative cell death, and apoptotic action in human breast cancer cells MCF-7 (Jaganathan et al., 2010b). Chrysin is another flavonoid found in honey that was tested in melanoma cells to enhance the apoptosis induced by p38 and Bax activation (Pichichero et al., 2011).

7.5 Considerations on oncological uses of honey

Honey is associated with longevity (Cooper et al., 2010) and can be seen as a medicine extending life beyond the term of the disease. The paradox remains for such a sugar rich food - considered as cancer promoter (Servan-Schreiber, 2009), when there is also evidence on the use of honey as an anticancer medicinal food and ingredient besides *Aloe arborescens* (Zago, 2004).

Nurses are directly involved in healthcare interventions, and have large contact with patients. Systematic reviews (SR) on the uses of honey within the oncological care come from nursing (Bardy et al., 2008; Gethin, 2008), subsequent to their exhaustive and recurrent contact with 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, 2008), and as potent antibacterial agents in cancer patients (Majtan et al., 2011).

Oncological uses of honey are directly involved with the antiproliferative properties acting as an anticancer drug, and to heal oncological wounds. There are too many botanic, geographic and entomologic origins of honey to ascribe the best curative option. They encompass fundamental factors that perform bioactive actions for individual to combined chemical structures.

Acknowledgements

Endeavour Awards from Australia for the 2011 Research Fellowship at the University of Sydney to Prof. P. Vit. To Dr. Silvia RM Pedro for careful reading of the manuscript references, and to Dr. David W Roubik for comments.

References

Abuharfeil N, Al-Oran R, Abo-Shehada M. 1999. The effect of bee honey on the proliferative activity of human B- and T-lymphocytes and the activity of phagocytes. Food and Agricultural Immunology 11: 169-177.

Ackland ML, van de Waarsenburg S, Jones R. 2005. Synergistic antiproliferative action of the flavonols quercetin and kaempferol in cultured human cancer cell lines. In Vivo 19: 69-76.

Acton C, Dunwoody G. 2008. The use of medical grade honey in clinical practice. British Journal of Nursing 17: S38-S44.

Attia WY, Gabry MS, El-Shaikh KA, Othman GA. 2008. The anti-tumor effect of bee honey in Ehrlich ascite tumor model of mice is coincided with stimulation of the immune cells. Egyptian Journal of Immunology 15: 169-83.

Bang LM, Buntting C, Molan P. 2003. The effect of dilution on the rate of hydrogen peroxide production in honey and its implications for wound healing. Journal of Alternative and Complementary Medicine 9: 267–273.

Bardy J, Slevin NJ, Mais KL, Molassiotis A. 2008. A systematic review of honey uses and its potential value within oncology care. Journal of Clinical Nursing 17: 2604-2623.

Biswal B, Zakaria A, Ahmad N. 2003. Topical application of honey in the management of radiation mucositis. A preliminary study. Supportive Care in Cancer 11: 242-248.

Bogdanov S. 2012. Honey in Medicine. http://www.bee-hexagon.net/files/file/fileE/HealthHoney/9HoneyMedicineReview.pdf 1-19.

Cantor D. 2008. Cancer in the Twentieth Century. The Johns Hopkins University Press. Baltimore, Maryland, USA; 350 pp.

Cavanagh D, Bfazley J, Ostapowicz F. 1970. Radical operation for carcinoma of the vulva. A new approach to wound healing. Journal of Obstetrics and Gynaecology of the British Commonwealth 77: 1037-1040.

Chanchao C. 2012. Bioactivity of honey and propolis of *Tetragonula laeviceps* in Thailand. In Vit P, Pedro S, Roubik DW, eds. Pot-honey: A legacy of stingless bees. Springer; Manila, Philippines (in press).

Chang X, Wang J, Yang S, Chen S, Song Y. 2011. Antioxidative, antibrowning and antibacterial activities of sixteen floral honeys. Food & Function 9: 541-546.

Cooper RA, Fehily AM, Pickering JE, Erusalimsky JD, Elwood PC. 2010. Honey health and longevity. Current Aging Science 3: 239-241.

Cutting KF. 2007. Honey and contemporary wound care: An overview. Ostomy Wound Management 53: 49-54.

D'Arcy BR. 2005. Antioxidants in Australian Floral Honeys –Identification of health-enhancing nutrient components. RIRDC Publication No 05/040. A report for the Rural Industries Research and Development Corporation; Barton, ACT, Australia. 84 pp.

Descottes B. Cicatrisation par le miel l'experience de 25 annees. Phitotherapie 7:112-116.

Fauzi AN, Norazmi MN, Yaacob NS. 2011. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. Food and Chemical Toxicology 49:871-878.

Forrest RD. 1982. Early history of wound treatment Journal of the Royal Society of Medicine 75: 198-205.

Ghashm AA, Othman NH, Khattak MN, Ismail NM, Saini R. 2010. Antiproliferative effect of Tualang honey on oral squamous cell carcinoma and osteosarcoma cell lines. BMC Complementary and Alternative Medicine 10: 49-56.

Gethin G. 2008. Commentary on Bardy J, Slevin NJ, Mais KL & Molassiotis A (2008) A systematic review of honey uses and its potential value within oncology care. Journal of Clinical Nursing 2008; 17: 2604-2623. Journal of Clinical Nursing 17: 2661-2664.

Gribel NV, Pashinkii VG. 1990. [The antitumor properties of honey]. Voprosy Onkologii 36:704-709.

Hamzaoglu I, Saribeyoglu K, Durak H, Karahasanoglu T, Bayrak I, Altug T, Sirin F, Sariyar M. 2000. Protective covering of surgical wounds with honey impedes tumor implantation. Archives of Surgery 135: 1414-1417.

Ibrahim AS. Antibacterial action of honey. 363-365 pp. Proceedings of the First International Conference on Islamic Medicine, Ministry of Health and the National Council for Culture, Arts and Letters, Kuwait, January. Bulletin of Islamic Medicine 2nd ed, vol. 1. 789 pp.

Irish J, Blair S, Carter DA. 2011. The antibacterial activity of honey derived from Australian flora. PLoS ONE 6: e18229. doi:10.1371/journal.pone.0018229

Jaganathan SK, Mandal M. 2009. Antiproliferative effects of honey and of its polyphenols. A review. Journal of Biomedicine and Biotechnology pp. 1-13.

Jaganathan SK, Mandal SM, Jana SK, Das S, Mandal M. 2010a. Studies on the phenolic profiling, anti-oxidant and cytotoxic activity of Indian honey: In vitro evaluation. Natural Product Research 24: 1295-1306.

Jaganathan SK, Mondhe D, Wani ZA, Pal HC, Mandal M. 2010b. Effect of honey and eugenol on Ehrlich ascites and solid carcinoma. Journal of Biomedicine & Biotechnology: ID989163 5 pp. doi:10.1155/2010/989163

Jones R. 2009. Honey and healing through the ages. Journal of ApiProduct and ApiMedical Science 1: 2- 5.

Jubri Z, Narayanan NNN, Karim NA, Ngah WZW. 2012. Antiproliferative activity and apoptosis induction by Gelam honey on liver cancer cell line. International Journal of Applied Science and Technology 4: 135-141.

Kampa1 M, Alexaki1 V-I, Notas G, Nifli1 A-P, Nistikaki1 A, Hatzoglou1 A, Bakogeorgou1 E, Kouimtzoglou E, Blekas G, Boskou D, Gravanis A, Castanas E. 2004. Antiproliferative and apoptotic effects of selective phenolic acids on T47D human breast cancer cells: potential mechanisms of action. Breast Cancer Research 6: R63-R74.

Kassim M, Achoui M, Mustafa MR, Mohd MA, Yusoff KM. 2010. Ellagic acid, phenolic acids, and flavonoids in Malaysian honey extracts demonstrate in vitro anti-inflammatory activity. Nutrition Research 30: 650-659.

Kwakman PHS, te Velde AA, de Boer L, Speijer D, Vandenbroucke-Grauls CMJE, Zaat SAJ. 2010. How honey kills bacteria. The FASEB Journal 24: 2576-2582.

Kwakman PHS, te Velde AA, de Boer L, Vandenbroucke-Grauls CMJE, Zaat SAJ. 2011. Two major medicinal honeys have different mechanisms of bactericidal activity. PLoS ONE 6: e17709. doi:10.1371/journal.pone.0017709

Kumar R, Lorenc A, Robinson N, Blair M. 2011. Parents' and primary healthcare practitioners' perspectives on the safety of honey and other traditional paediatric. Child Care Health and Development 37:734-43.

Liberato MCTC, De Morais SM, Siqueira SM, de Menezes JE, Ramos DN, Machado LK andMagalhaes IL. 2011. Phenolic content and antioxidant and antiacetylcholinesterase properties of honeys from different floral origins. Journal of Medicinal Food 14: 658-663.

Lund-Nielsen B, Adamsen L, Kolmos HJ, Rorth M, Tolver A, Gottrup F. 2011. The effect of honey-coated bandages compared with silver-coated bandages on treatment of malignant wounds randomized study. Wound Repair & Regeneration 19: 664-70.

Lusby PE, Coombes AL, Wilkinson JM. 2005. Bactericidal activity of different honeys against pathogenic bacteria. Archives of Medical Research 36: 464–467

Majtan J, Majtanova L, Bohova J, Majtan V. 2011. Honeydew honey as a potent antibacterial agent in erradication of multi-drug resistant *Stenotrophomonas maltophilia* isolates from cancer patients. Phytotherapy Research 25: 584-587.

Molan PC. 1999. Why honey is effective as a medicine. 1. Its use in modern medicine. Bee World 80: 80-92.

Molan PC, Russell KM. 1988. Non-peroxide antibacterial activity in some New Zealand honeys. Journal of Apicultural Research 27: 62-67.

Moolenaar M, Poorter RL, van der Toorn PPG, Lenderink AW, Poortmans P, Egberts ACG. 2006. The effect of honey compared to conventional treatment on healing of radiotherapy-induced skin toxicity in breast cancer patients. Acta Oncologica 45: 623-624.

Moore OA, Smith LA, Campbell F, Seers K, McQuay HJ, Moore RA. 2001. Systematic review of the use of honey as a wound dressing. Biomed Central Complementary and Alternative Medicine 1-4.

Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, Omidi S. 2008. The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial. Journal of Contemporary Dental Practice 9: 40-47.

Pichichero E, Cicconi R, Mattei M, Canini A. 2011. Chrysin-induced apoptosis is mediated through p38 and Bax activation in B16-F1 and A375 melanoma cells. International Journal of Oncology 38: 473-483.

Pichichero E, Cicconi R, Mattei M, Muzi MG, Canini A. 2010. Acacia honey and chrysin reduce proliferation of melanoma cells through alterations in cell cycle progression. International Journal of Oncology 37: 973-981.

Qu'ran. An Islamic perspective on the bee. http://www.islamawareness.net/Animals/bee.html

Radojcic, I., Berkovic, K., Kovac, S., Vorapik-Furac, J. (2008). Natural honey and black radish juice as tin corrosion inhibitors. Corrosion Science 50, 1498-1504.

Robson V. 2002. Leptospermum honey used as debriding agent. Nurse to Nurse 2:66-68.

Romier B, Van De Walle J, During A, Larondelle Y, Schneider YJ. 2008. Modulation of signaling nuclear factor-κB activation pathway by polyphenols in human intestinal CACO-2 cells. British Journal of Nutrition 100: 542-541.

Samarghandian S, Tavakkol Afshari JT, Davoodi S. 2011. Honey induces apoptosis in renal cell carcinoma. Pharmacognosy Magazine 7: 46-52.

Servan-Schreiber D. 2009. Anticancer: A new way of life. Penguin, New York, USA; 274 pp.

Sharp A. 2009. Beneficial effects of honey dressings in wound management. Nursing Standard 24: 66-74.

Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. 2007. How quickly do systematics reviews go out of date?. A survival analysis. Annals of Internal Medicine 147: 224-233.

Simon A, Sofka K, Wiszniewsky G, Blaser G, Bode U, Fleischhack G. 2006. Wound care with antibacterial honey (Medihoney) in pediatric hematology-oncology. Supportive Care in Cancer. 14: 91-7.

Tan MK, Hasan Adli DS, Tumiran MA, Abdulla MA, Yusoff KM. 2012. The efficacy of Gelam honey dressing towards excisional wound healing. Evidence-Based Complementary and Alternative Medicine 1-6 pp. doi:10.1155/2012/805932.

Templeton S. 2005. Management of chronic wounds: the role of silver-containing dressings. Primary Intention 13: 170-179.

Tonks A, Cooper RA, Price AJ, Molan PC, Jones KP. 2001. Stimulation of TNF-alpha release in monocytes by honey. Cytokine 14: 240-242.

Vit P, Yu J, Huq F. 2012. Use of honey in cancer prevention and therapy. 481-493 pp. In Vit P, Pedro S, Roubik DW, eds. Pot-honey: A legacy of stingless bees. Springer; New York, USA. 654 pp.

Yoon YM, Newlands C. 2005. Quality standards of medical grade Manuka honey. 89-102 pp. In White RJ, Molan P, Cooper RA eds. Honey: A modern wound management product. Wounds UK; Aberdeen, UK 160 pp.

White JW, Subers MH, Schepartz AI. 1963. The identification of inhibine, the antibacterial factor in honey, as hydrogen peroxide and its origin in a honey glucose-oxidase system. Biochimica et Biophysica Acta 73: 57-70.

White R. 2005. The benefits of honey in wound management. Nursing Standard 20: 57-64.

Wiszniewsky G, Sofka K, Simon A, Bode U, Blaser G, Fleischhack G. 2006. Wound care with antibacterial honey (Medihoney) in pediatric hematology-oncology. Supportive Care in Cancer 14: 91-97.

Wen CT, Hussein SZ, Abdullah S, Karim NA, Makpol S, Mohd Yusof YA. 2012. Gelam and Nenas honeys inhibit proliferation of HT29 colon cancer cells by inducing DNA damage and apoptosis during inflammation control. Asian Pacific Journal of Cancer Prevention 13: 1605-1610.

Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, McCabe MG, Meyer S, Khalid T. 2010. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews 4: 978.

Zago R. 2004. Di cancro si può guarire. OFM. Edizioni Adle; Padova, Italia. 160 pp.

Zerm R. 2012. IntegrativeBehandlung chronischer Wunden unter besonderer Berucksichtigung des Honigs. Der Merkurstab 65: 4-11.

Zidan J, Shetver L, Gershuny A, Abzah A, Tamam S, Stein M, Friedman E. 2006. Prevention of chemotherapy-induced neutropenia by special honey intake. Medical Oncology 23: 549-552.

Zumla A, Lulat A. 1989. Honey a remedy rediscovered. Journal of the Royal Society of Medicine 82: 384-385.

how to cite this chapter?

Vit P, Huq F. 2013. Systematic reviews on interventions with honey in cancer. pp. 1-9. In Vit P & Roubik DW, eds. Stingless bees process honey and pollen in cerumen pots. Facultad de Farmacia y Bioanálisis, Universidad de Los Andes; Mérida, Venezuela. http://www.saber.ula.ve/handle/123456789/35292