Sains Malaysiana 47(11)(2018): 2705–2711
http://dx.doi.org/10.17576/jsm-2018-4711-14

Malaysian *Tualang* Honey and Its Potential Anti-Cancer Properties: A Review

(Madu Tualang Malaysia dan Potensi Sifat Anti-Kansernya: Suatu Kajian)

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ABSTRACT

The use of honey as a therapeutic agent dates back at 8000 years and has markedly increased interest into its potential health benefits. The by-products of the flower nectar have a complex chemical composition which promotes benefits in underlying mechanism of human diseases. Malaysian Tualang *Honey (MTH) is a multifloral jungle honey produced by the rock bee (*Apis dorsata*). This review consolidates the results of carious studies involving biochemical assays of tissue culture and animal trials of anti-cancer properties of MTH. Often studied in the context of breast cancer cell lines, MTH has promising data for possible mechanisms in anti-cancer activity. These include apoptosis via depolarization of the mitochondrial membrane, caspase-dependent apoptosis, reduction of angiogenesis and the promotion of cell cycle arrest without posing cytotoxic effect on normal cell lines. Despite positive outcomes in tissue cultures, the oral administration of MTH in breast cancer animal models showed slower tumour progression, reduction in tumour size and better grading of histological features. The alleviation of breast carcinogenesis via modulation of hematologic, estrogenic and apoptotic activities promotes MTH as a promising anticancer agent. With confidence in a conclusion that MTH is a useful treatment for cancer, further experimental and clinical studies should be conducted.*

Keywords: Anti-cancer; anti-proliferative; breast cancer; Malaysian Tualang *Honey*

ABSTRAK

*Penggunaan madu sejak 8000 tahun yang lalu sebagai agen terapeutik telah meningkat dengan ketara kerana potensi manfaatnya kepada kesihatan. Produk sampingan daripada nektar bunga ini mempunyai komposisi kimia yang kompleks dan menpromosikan manfaat untuk mengubati penyakit manusia pada peringkat asas mekanisme penyakit tersebut. Madu Tualang Malaysia (MTH) adalah madu hutan pelbagai jenis flora yang dihasilkan oleh lebah Tualang, lebah madu gergasi atau dikenali sebagai naning (*Apis dorsata*). Kertas ini melaporkan keputusan pelbagai kajian yang melibatkan ujian biokimia untuk menguji sifat anti-kanser MTH yang dijalankan terhadap kultur tisu dan model haiwan. Kajian yang dijalankan ke atas sel selanjar kanser payudara menunjukkan bahawa MTF mempunyai aktiviti anti-kanser. Perkara ini termasuklah apoptosis melalui depolarisasi membran mitokondria, apoptosis bersandarkan-caspase, pengurangan angiogenesis dan pemberhentian kitaran sel tanpa mempunyai kesan sitotoksik terhadap sel selanjar normal. Walaupun kesan positif MTF terhadap kultur sel, pemberian MTH secara oral kepada model kanser payudara haiwan menunjukkan bahawa MTH memperlahankan perkembangan tumor, mengurangkan saiz tumor dan membaiki gred histologi sel tumor. Kesan MTH terhadap pengurangan karsinogenesis payudara melalui modulasi aktiviti hematologi, estrogen dan apoptosis memungkinkan MTH menjadi agen anti-kanser yang berpotensi. Untuk memperoleh keputusan yang lebih meyakinkan bahawa MTH boleh menjadi rawatan yang berguna untuk kanser, uji kaji lanjutan dan kajian klinikal perlu dilakukan.*

Kata kunci: Anti-kanser; anti-proliferasi; kanser payudara; Madu Tualang Malaysia

INTRODUCTION

About 14.1 million new cases and 8.2 million patient deaths from cancer were reported in 2012 globally (Cancer Research UK 2018). A total of 100,000 new cancer cases were diagnosed in Malaysia for the period of 2007 - 2011 (Asmah et al. 2016). Lung, female breast, bowel and prostate cancers were the most prevalent worldwide (World Health Organization 2018). Breast, colorectal and lung cancers are the most common among Malaysians (Asmah et al. 2016). The number is still rising every year and shows no signs of decrease, even with advancements in medical technology. Responsible for 8.8 million deaths in 2015 (World Health Organization 2018), cancer is the second leading cause of death globally. The economic impact of cancer is definitely significant and is increasing every year. These numbers demonstrate that cancer is a major public health problem worldwide.

Cells are the body basic building blocks and the body constantly makes new cells to heal injuries and help us to grow and replace worn-out tissue via an ordered series of cell division events which is strictly regulated. In the case of abnormal cell formation due to DNA damage caused by free oxygen radicals or exposure to external sources of ionizing radiation in the environment, the cell division processes may be halted or undergo programmed cell death (Deckbar et al. 2011). If abnormal cells cannot be stopped

from growing and instead continue to expand rapidly beyond normal limit (uncontrolled cell division) and spread throughout the body (metastasis), this becomes a pathological condition known as cancer (Nosrati et al. 2017). Various therapeutic approaches to treat cancer have been introduced to lower the mortality rate of cancer patients, including radiation therapy, surgery, chemotherapy, hormone therapy and immunotherapy. Although the high doses of radiation used in radiotherapy may kill cancer cells and effectively prevent relapse (Sudhakar 2009), this will affect the surrounding healthy cells. The commonly known side effects are fatigue, hair loss, nausea and vomiting and skin changes (Bentzen 2006), which can severely compromise patients' quality of life. Surgical removal of local tumors may be another option to battle the morbidity and mortality caused by cancer (Abdulrasheed et al. 2011). However, surgery is not suitable for certain metastatic cancer types such as leukemia. Chemotherapy is used to treat cancers, frequently in combination with other treatment strategies. Nevertheless, similar to radiation therapy, chemotherapy may damage healthy cell and eventually lead to adverse effects (Raji 2005).

Hormone are natural substances secreted by endocrine gland which are essential to coordinate growth and activity of cells and organ functions as a system. Hormone therapy may slow or stops the growth of cancer cells that relies on it, such as prostate and breast, but it also affects the normal body functions. For instance, tamoxifen is used to block estrogen receptors on breast cancer cells; on the other hand, it may cause serious side effects even though rare, such as blood clots (Hernandez et al. 2009) and increased risk of developing uterine cancer for post- menopausal women (Hu et al. 2015). In addition to the therapies mentioned previously, immunotherapy also used in fighting cancer. It is a type of biological therapy which helps the immune system to fight against the cancer cells (Pardoll 2012). Unfortunately, this type of treatment can lead to imbalances in immunologic tolerance, manifesting as immune-related adverse events. Numerous autoimmune toxicities in different organs have been reported, including the skin, lungs, kidneys and heart (Michot et al. 2016).

Due to the mentioned risks, many cancer patients seek alternative and/or complementary methods to treat cancer. This has led to the search for a new therapeutic agent to fight against cancer with minimum or less adverse. Biodiverse natural products offer great opportunities for innovative drug discovery, as they produce a wide spectrum of therapeutic active chemical compounds. Small organic molecules derived from natural products have been used as cancer chemotherapeutic drugs, such as paclitaxel, vinblastine and vincristine. These small organic compounds are not only derived from plants, but also can be found in microbes, marine fauna and flora and even honey (Mann 2002). Compounds with desired properties such as high availability of source, less side effects and effective drug interactions drivers for scientists to explore and discover new anticancer agents from natural products (Nussbaumer et al. 2011; Sakarkar & Deshmukh 2011).

HONEY

Honey has been used as a therapeutic agent since the beginning of historical records dating back to around 8000 years ago (Eteraf-Oskouei & Najafi 2013). The use of honey underwent a transformation from folk remedy to scientific investigation in the late 19th century. The first documented research into the medical usages of honey was by Van Ketel in 1892. He indicated the antimicrobial properties of honey. Further research was done in United States and Europe (Dustmann 1979). Studies have shown that people have long believed that consumption of honey can improve the digestive system (El-Arab et al. 2006). In India, honey is used as a remedy to cure cough and to maintain good dental health (Eteraf-Oskouei & Najafi 2013). Furthermore, honey was also among the most popular remedies in ancient Egypt as reported by Eteraf-Oskouei and Najafi (2013) and was used as the main ingredient in therapy. During that time, honey was commonly used as a topical ointment to improve wound healing and as an antiseptic agent (Riddle 2014). There are hundreds of types of honey produced around the world and their identity depends on the floral sources unique to a particular region (Kaškonienė & Venskutonis 2010). The basic makeup of honey is water content, floral sources, sugars and the proportion of specific amino acids, organic acids, enzymes, proteins and phytochemicals (Ball 2007). Honey is 80-85% of fructose and glucose and can serve as viscous natural sweetener (Rao et al. 2016). The water content of honey varies due to environmental factors such as the humidity around and inside the hives (Olaitan et al. 2007). Honey composition is also affected by temperature and storage locations (Stephens et al. 2015). Most honey has similar ingredient phenolic acids, such as caffeic, ferulic and *p*-coumaric acids; flavonoids, such as apigenin, galangin and kaempferol, as well as antioxidants such as tocopherols, ascorbic acids, GSH (reduced glutathione), CAT (catalase) and SOD (superoxide dismutase), but varies in its proportions (Rao et al. 2016). Every component of honey has unique medicinal and nutritional properties and can be applied according to patient needs.

The various compositions of phytochemicals with high flavonoid and phenolic content of honey make it an effective antioxidant (Iurlina et al. 2009) and a potent scavenging agent (Kishore et al. 2011). Studies have shown that a darker colour may indicate higher phenolic content and also strong antioxidant activity (Estevinho et al. 2008). Flavonoid and phenolic compounds biological activities within it have proven to be natural immune booster too. Despite this evidence about the effects of flavonoid, phenolic compounds and polyphenols on immune function, the underlying mechanisms are not fully understood.

Apart from the immune system, agents with strong antioxidant properties may prevent tumour development.

Excessive production of free radicals and reactive metabolites has been known to cause tumour formation (Valko et al. 2007). However, our body possesses endogenous mechanisms to eradicate damaging free radicals with help from consumed antioxidants from vegetables or fruits which contains high concentration of flavonoid and phenolic compounds. Recently, flavonoids have gained tremendous attention due to its anti-cancer properties. The known underlying mechanism of actions includes the inhibition activity of tumour cells proliferation, induction of cell apoptosis (Ghashm et al. 2010), inhibition of lipoprotein oxidation (Gheldof & Engeseth 2002) as well as promoting cell cycle arrest (Pichichero et al. 2010). Honey is known to have high levels of flavonoids (Gomez-Caravaca et al. 2006) which are beneficial for combating cancer. A recent study documented that Malaysian *Tualang* Honey has significant anti-cancer properties against several cancer cell lines (Fauzi et al. 2011; Ghashm et al. 2010). Honey has also been shown to induce early apoptosis (Ghasm et al. 2010) in addition to late apoptosis (Fauzi et al. 2011) through disruption of the mitochondrial membrane (Fauzi et al. 2011).

TYPES OF MALAYSIAN HONEY

Malaysia has only 0.2% of the world's land mass; however, the tropical rainforests, seas and freshwater ecosystems of Malaysia support a rich and diverse array of both flora and fauna. Indeed, the flora of the Malaysian rainforest is among the richest in the world and harbours many different types of honey. Each honey contains a unique combination of chemical constituents, thus, exhibits multi-biological activities. This is mainly due to its geographical floral origin, climatic condition, environmental factors and treatment of beekeepers (Kaškonienė et al. 2010). Table 1 shows the main types of honey found in Malaysia.

MALAYSIAN *TUALANG* HONEY

Malaysian *Tualang* Honey (MTH) is a multifloral jungle honey found in the tropical rainforests of Peninsular Malaysia, southern Thailand, northern Sumatra and Borneo (Ahmed & Othman 2013). The honey is produced by the giant Asian rock bees named *Apis dorsata*. Their disk-shaped hives are built on the horizontal branches of Menggaris tree (*Koompassia excelsa*) (Ahmed & Othman 2013). This tree belongs to the Fabaceae family and is very common in the tropical rainforests Malaysia (Ahmed & Othman 2013). *Tualang* honey has generally a dark brown appearance which correlates with its high phenolic content (Ahmed & Othman 2013). Studies have also shown that the phenolic content in MTH is much higher than other types of honey (Kishore et al. 2011). High performance liquid chromatography (HPLC) has shown the presence of a number of phenolic acids, including gallic, syringic, benzoic, trans-cinnamic, p-coumaric acids and flavonoid compounds such as catechin and kaempferol in MTH (Khalil et al. 2011). On the other hand, Tan et al. (2014) reported MTH contains 5-(hydroxymethyl)-2-furancarboxaldehyde, 3-furaldehyde, 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-, phenylacetaldehyde, 2-furanmethanol and maltol which known to contribute antioxidant properties of this honey. Due to a number of phytochemical constituents, accumulating evidence supports that MTH possesses multiple biological activities, including antimicrobial, anti-inflammatory, antioxidant, antimutagenic, antitumor properties and also promotes wound healing (Attia et al. 2008; Fauzi et al. 2011; Ghashm et al. 2010; Halima et al. 2010; Mohamed et al. 2010; Nasir et al. 2010).

ANTI-CANCER PROPERTIES OF MALAYSIAN *TUALANG* HONEY

Malaysian *Tualang* Honey (MTH) may have the potential as a natural cancer 'killer' due multi-biological activities. The possible anti-cancer activities of MTH seem to have involved multiple mechanisms for instance, through apoptotic, antiproliferative, anti-oxidant and anti-inflammatory pathways. Studies have been performed to test MTH against difference cancer cell lines. Fauzi et al. (2011) first reported that MTH is capable of inducing apoptosis in human breast cancer cell line (MCF-7). The apoptotic effect was associated with depolarization of the mitochondrial membrane in the MCF-7 cell line. Mitochondria serve as an energy (ATP) generator and metabolites for the building of macromolecules and reactive oxygen species (ROS). This process is vital in cell viability and proliferation. However, mitochondrial dysfunction has been reported in cancer cells (Hsu et al. 2016), which cause major changes in cellular energy metabolism and excessive production of ROS. This will affect cell fates and drug responses (Wen et al. 2013). Data have shown that MTH affects mitochondrial membrane of the MCF-7 cell line, hence providing another adjunct treatment in cancer therapy to kill cancer cell.

TABLE 1. Types of Malaysian honey, floral type and sources

Name of honey	Floral type (bee species)	Local (scientific) tree name
Acacia honey	Monofloral *(Apis mellifera)*	Forest mangrove or mangium tree *(Acacia mangium)*
Pineapple honey	Monofloral *(Apis mellifera)*	Pineapple *(Ananas comosus)*
Borneo honey	Monofloral *(Apis cerana)*	Forest mangrove or Mangium tree *(Acacia mangium)*
Kelulut honey	Multifloral *(Trigona* spp.*)*	Hollow tree
Gelam honey	Monofloral *(Apis mellifera)*	Mangrove/ Gelam tree (*Melaleuca cajuputi*)
Tualang honey	Multifloral *(Apis dorsata)*	*Tualang* tree *(Koompassia excelsa)*

(From Moniruzzaman et al. 2013 and Zainol et al. 2013)

Additionally, activation of caspase-3/7 and -9 were also observed in MTH-treated MCF-7 cell line (Fauzi et al. 2011).

Another group also documented that combination of MTH and tamoxifen were more effective in inhibiting cell growth of both breast cancer cell lines, oestrogen receptor-dependent MCF-7 and oestrogen receptor-independent MDA-MB-231 (Yaacob et al. 2013). Based on the data from flow cytometric analysis, the inhibition mechanism involved induction of caspase-dependent apoptosis, including caspase-3/7, -8 and -9. Long-time consumption of tamoxifen can leads to potential health side effects, including increase the patient's risk of developing endometrial cancer (Fisher et al. 1994). Evidence has demonstrated that natural products have beneficial effects in reducing side effects induced by cancer chemotherapy. For example, Rikkunshito, a traditional Japanese herbal medicine, is capable to suppress cisplatin-induced anorexia in humans (Ohno et al. 2011). Goshajinkigan is a herbal medicine which composed of 10 natural products prevent oxaliplatin-induced neurotoxicity (Yoshida et al. 2013). This suggests that MTH not only has the potential to be a cancer prevention supplement but also as an adjuvant for the chemotherapeutic agent to reduce the side effects induced by anti-cancer drugs. Apart from that, it also enhances the effectiveness of the current treatment.

To further understand the anticancer mechanism of action of MTH, Fauzi and Yaacob (2016) examined the effects of MTH on cell cycle regulation and apoptosis-related molecules in both human oestrogen receptor (ER) α-positive MCF-7 and (ER) α-negative MDA-MB-231 breast cancer cell lines. They demonstrated that MTH significantly induced growth inhibition and induction of apoptosis for both of the breast cancer cell lines. Surprisingly, the apoptotic effect of MTH is different in both of the cancer cell lines: MTH caused G2/M phase arrest in MCF-7 cell line, however S phase arrest in MDA-MB-231 cell line. MTH also up-regulated the expression of p53, p21 and FADD in MCF-7 cell line; and TRADD, FADD and p21 in MDA-MB-231 cell line (Fauzi & Yaacob 2016). Taken together, this suggests that MTH affects proliferation of MCF-7 and MDA-MB-231 breast cancer cell line via different signalling cascade.

The cause of cancer is multifactorial, as it can be a result of genetic alterations. Susceptibility genes account for less than 25% of family risks in breast cancer (King et al. 2003). Additionally, Epstein - Barr virus infection (Glaser et al. 2004), radiation exposure, exogenous hormones such as hormone replacement therapy (Million Women Study Collaborators 2003) and early onset of menarche and late onset of menopause (Hsieh et al. 1990) have been reported to increase the risk of breast cancer formation. One of the strategies in breast cancer therapy and prevention is a drug that capable of targeting multiple anti-cancer pathways. Interestingly, studies demonstrated that oral administration of MTH to MNU-induced breast cancer-bearing animals caused slower tumour progression, reduction in tumour size and better histological features and grading and alleviates breast carcinogenesis via modulation of hematologic, estrogenic and apoptotic activities, via lowering anti-apoptotic proteins expression and up-regulating pro-apoptotic protein expression (Ahmed & Othman 2017; Ahmed et al. 2017). Moreover, Kadir et al. (2013) tested MTH in rats with induced breast cancer using 7, 12-dimethylbenz (α) anthracene (DMBA). Treatment with MTH via oral gavage daily for 150 days following oral administration of DMBA significantly reduced number, volume and weight, with better histological grade and morphology of cancer in breast cancer-bearing rats compared to the control group. Furthermore, the MTH-treated group showed higher activity of apoptotic as well as reduced level of angiogenesis. Collectively, data showed that MTH capable in slowing down the progression of cancer formation.

There are many types of cancer treatments available, including surgery, radiation therapy, immunotherapy and stem cell transplants, as well as chemotherapy. However, the side effects develop from the treatments are the main concern for all the cancer patients. Chemotherapy drugs are widely used as anti-cancer therapies and they are targeting on proliferating cells through a distinct and cell cycle-dependent mechanism (Dy & Adjel 2008). Chemotherapy drugs are able to kill cancerous cells and cause a tumour to shrink. Unfortunately, most of the chemotherapy drugs not only attack cancerous cells but also healthy cells and their cytotoxicity for many types of dividing cells frequently lead to detrimental effects, such as immunosuppression, organ dysfunction and cognitive impairment (Hudson et al. 2013; Schünemann et al. 2008). Treatments which are capable of killing only cancer cells but not healthy cells are favorable to cancer patients. MTH has proved to be toxic only to breast cancer cell line, MCF-7 but not normal and healthy breast cell (MCF-10A) (Fauzi et al. 2011; Yaacob & Ismail 2014). In addition, it also increases expression of DNA repair proteins, such as Ku70 and Ku80 in MCF-10A (Yaacob & Ismail 2014).

In addition to breast cancer, MTH has also been documented as effective anti-cancer agent against several types of cancer cell lines, including cervical cancer cell (HeLa) (Fauzi et al. 2011), oral squamous cell carcinoma (CRL-1632), human osteosarcoma (CRL-1543) (Ghashm et al. 2010), acute human leukemia cell line (K562) and chronic human leukemia cell line (MV4-11) (Man et al. 2015). It is suggested that MTH promoted early apoptosis in these cancer cell lines which attributed to its anti-cancer properties. Table 2 summarizes the anti-cancer activities of MTH including its mode of action.

Conclusion

MTH is rich with phenolic compounds and thus has higher antioxidant levels than other types of honey. There has been a surge of interest towards this honey on its potential health benefits such as anti-inflammatory, wound healing, anti-bacterial as well as anti-cancer properties. It is believed that its high antioxidant levels lead to multiple pharmacological activities including anti-cancer activity. With the data mentioned, it is postulated that MTH is a source of anti-cancer agents and an adjuvant for chemotherapeutic agents.

TABLE 2. Anti-cancer properties of MTH and its mode of action

Type of cancer	Experiment setting (Cell line/ Animal)	Mode of action	Reference
Breast cancer	• MCF-7 cell line	• Apoptotic effect associated with depolarization of the mitochondrial membrane • Activation of caspase-3/7 and -9	Fauzi et al. (2011)
Breast cancer	• MCF-7 • MDA-MB-231	• Activation of caspase-3/7, -8 and -9 • Depolarization of the mitochondrial membrane • Reducing tamoxifen-induced adverse effects	Yaacob et al. (2013)
Breast cancer	• MCF-7 • MDA-MB-231	• Caused G2/M phase arrest in MCF-7 • Up-regulated p53, p21 and FADD in MCF-7 • Caused S phase arrest in MDA-MB-231 • Up-regulated TRADD, FADD and p21 in MDA-MB-231	Fauzi & Yaacob (2016)
Breast cancer	• MNU-induced breast cancer in rats	• Ameliorating haematological and serological parameters • Up-regulated caspase-9, Apfa-1, p53, IFN-γ, IFNGR1 • Down-regulated Bcl-xL, TNF-α, COX-2, E2 and ESR1	Ahmed et al. (2017); Ahmed & Othman (2017)
Breast cancer	• DMBA-induced breast cancer in rats	• Reduced the number, volume and weight of tumor • Improved histological grade and morphology of tumor • Increased apoptotic activity • Reduced level of angiogenesis	Kadir et al. (2013)
Oral squamous cell carcinoma	• CRL-1632	• Induced early apoptosis • Inhibited proliferation	Ghashm et al. (2010)
Osteosarcoma	• CRL-1543	• Induced early apoptosis • Inhibited proliferation	Ghashm et al. (2010)
Acute myeloid leukemia	• MV4-II	• Induced apoptosis	Man et al. (2015)
Chronic myeloid leukemia	• K562	• Induced apoptosis	Man et al. (2015)
Cervical cancer	• HeLa	• Apoptotic effect associated with depolarization of the mitochondrial membrane • Activation of caspase-3/7 and -9	Fauzi et al. (2011)

Further laboratory research, such as tests on different cancer cell lines or cancer-bearing animals and other cancer signaling pathway including microenvironment of tumor, should be conducted. In addition, clinical trials on human cancer patients are also needed, for instance randomized controlled trials (RCTs) (or randomized comparative trials) which currently serve as the gold standard for most clinical trials and capable to provide the best evidence of the efficacy of healthcare interventions. These definitely will help inafte fully understand the anti-cancer mechanism exhibited by MTH.

ACKNOWLEDGEMENTS

The research was supported by the Fundamental Research Grant Scheme (FRGS), Ministry of Higher Education, Malaysia with project number FRGS/1/2016/SKK08/UPM/02/10 (04-01-16-1811FR). In addition, we would like to thanks Dr. Nizar Abd Manan for the Malay language editing.

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Received: 8 March 2018
Accepted: 30 July 2018