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REVIEW ARTICLE

Gelam Honey: A Review of Its Antioxidant, Anti-inflammatory, Anticancer and Wound Healing Aspects

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ABSTRAK

Beberapa tahun kebelakangan ini kecenderungan kajian terhadap madu didapati meningkat dengan meluasnya apabila ia telah dikenalpasti mempunyai potensi untuk memberi manfaat kepada kesihatan, pencegahan penyakit dan berfungsi sebagai penggantian perubatan moden. Madu merupakan produk bahan gula semulajadi yang dihasilkan oleh lebah madu dari nektar bunga dan telah digunakan untuk merawat beberapa jenis penyakit seperti penyakit kardiovaskular, kencing manis, kanser, dan penyakit Alzheimer's sejak zaman purba. Madu Gelam merupakan salah satu madu monofloral liar Malaysia yang sering digunakan secara meluas sebagai bahan perubatan tradisional dalam kalangan penduduk tempatan. Madu Gelam diperkayai dengan beberapa ciri-ciri terapeutik seperti anti-pengoksidaan, anti-radang, anti-kanser dan meningkatkan tahap penyembuhan luka. Walau bagaimanapun, terdapat kekurangan sastera yang memberi tumpuan kepada kesan keseluruhan Madu Gelam dan nilai perubatannya. Kertas kajian ini meringkaskan ciri-ciri fotokimia Madu Gelam berserta dengan nilai-nilai terapeutik yang membawa kepada peningkatan spektrum idea yang luas terhadap produk kesihatan semulajadi. Penjelasan yang ringkas didokumenkan terhadap ciri-ciri terapeutik Madu Gelam untuk memberi pengetahuan baru kepada masyarakat saintifik di dalam era globalisasi moden kini.

Kata kunci: antioksidan, antikanser, anti-radang, gelam madu, penyembuhan luka

ABSTRACT

In recent years, there is a growing enthusiasm in honey which has potential health benefits, disease prevention and serves as substitution of modern medicine. Honey is a natural sweet product which is produced by honey bees from floral nectar and has been traditionally used to treat several diseases such as cardiovascular

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disease, diabetes mellitus, cancer and Alzheimer's disease since ancient times. Gelam honey (GH) is one of the Malaysian wild monofloral honey which is widely used as traditional medicine by the local population. GH is enriched with several therapeutic properties namely, antioxidative, antiinflammatory, anticancer and accelerated wound healing activities. However, there is lack of literature focusing on the overall effects of GH and its medicinal value. This review paper summarises the phytochemistry characteristics of GH along with its therapeutic values which lead to a broad spectrum idea on several diseases. A concise clarification on the therapeutic properties of GH is expected to provide new knowledge to the scientific society in the era of modern globalization.

Keywords: anticancer, anti-inflammatory, antioxidant, gelam honey, wound healing

INTRODUCTION

Honey, a part of ancient medicine, has recently become the key target of attention for treating certain diseases, promoting overall health and well being. Honey is known as natural sweet substance made from honey bees from floral nectar. Honey is commonly used to treat many ailments (Wen et al. 2012). Since ancient times, various types of honey and their derivatives are being used to treat several diseases such as cancer, infections, delayed wound healing, etc (Hussein et al. 2012). The knowledge on traditional usage of honey has been verbally passed through generations to generations. Thus, honey draws attention of many researchers. The information on the therapeutic values of honey was aimed to proceed with further researches. Consequently, it stimulated the several scientific studies on specific honey to verify the claims of community people on their medicinal value.

Gelam Honey (GH) is one of Malaysian wild monofloral honeys produced by Apisdorsata bees. The main nectar as well as the pollen collected by the bees are from the plant named *Melaleucacajupati Powell* or locally known as the "Gelam tree". The plant belongs to the *Myrtaceae* family. GH is produced in large amounts in the state of Terengganu on the eastern coast of peninsular Malaysia, where these mangrove trees grow abundantly (Moniruzzaman et al. 2013a). GH is usually prepared by base hydrolysis and extracted with ethyl acetate (Wahdan 1998). Locally in Malaysia, the timber of gelam is known as kayu putih and has a tall evergreen tree of 24 meter height. In Malaysia, the species of Melaleuca grow naturally in swamp forests behind the sandy beaches and the mangroves in the states of Kedah, Melaka, Negeri Sembilan, Kelantan and Terengganu. The trees are well recognised by their characteristic thick papery flaky bark (Lim & Midon 2001). The common English name for Gelam tree differs from place to place and often known as the "swamp tea-tree" and also referred to as the "paperback tea-tree" and the "cajeput" tree (Ng 1978). The

Table 1: Physiochemical properties of Gelam honey (GH) (A-Rahaman et al. 2013)

Physiochemical properties	Values (Mean ± SD)
pH	3.52 ± 0.07
Colour (mm Pfund)	139.00 ± 0.00
Moisture (%)	24.07 ± 0.12
Electrical Conductivity, (mS/cm)	1.02 ± 0.0089
Total soluble solid, (%)	74.07 ± 0.15

purpose of present review is to provide the current therapeutic information of GH and its usage in medical research along with complete overview of its phytochemistry, traditional uses, and pharmacological values. In addition, the present review summarise evidence-based findings on GH and its therapeutic properties, which will help to propose future research prospects.

TRADITIONAL USES OF GELAM HONEY

In Malaysia, oral administration of GH is used to treat the cholera. Its topical application is for the treatment for thrush, vaginal infection, acne, athlete's foot, verruca, warts, insect bites, cold sore and nits. In Myanmar, GH is purified from the leaves to treat gout. The Indochinese uses cajuput oil for rheumatism and applied as analgesic whereas the oil is used externally in Indonesia for burns, colic, cramps, earache, headache, skin diseases, toothache and wounds. In Philippine, the leaves are used to treat asthma. When administered orally, it induces sweating and acts as antispasmodic (Koh et al. 2009). The papery barks of Gelam trees are used for caulking wooden boat (Lim & Midon 2001).

PHYSIOCHEMISTRY AND CHEMICAL COMPOSITION OF GH

A physiochemical property of honey is very important as its characteristic contribute to the production of quality honey. The physiochemistry of GH from the previous studies was shown in Table 1 (A-Rahaman et al. 2013). The pH value of GH was acidic in nature. The pH value represents the stability against microbial spoilage, life expectancy of honey product and fermentation process (Silva et al. 2013; Bogdanov 1997). GH was reported to have dark colour with Pfund scale of 139.00 mm. The color of GH was categorized as light amber to dark amber (The National Honey Board 2003). The colour of GH was due to the presence of some pigments such as chlorophylls, carotenoids, flavonoids and derivatives of tannins and polyphenols (Juszczak et al. 2009). GH was reported to have high moisture content (up to 20%). The moisture content denotes the quality and shelf-life of honey product. The factor of storage combined with the high moisture content in honey increase the fermentation rate, and result in formation of acidified honey. Moreover, the moisture content of

(a)

(b)

(c)

(d)

Figure 1: a) whole plant of Gelam tree b) Gelam 'papery' and flaky bark c) leaves of Gelam tree d) brown capsules of Gelam fruits (Burkill 1993)

honey highly depends on climatic change, maturity of honey and its harvesting season (Finola et al. 2007). A group of researchers observed that the moisture content indicates the origin of honey. In a tropical country like Malaysia with rainy season all over the year leads high moisture content in GH. Thus, Malaysian honey is always treated by evaporation to reduce the water content and to increase the quality.

PHYTOCHEMICAL COMPOSITION OF GELAM HONEY

Honey was reported to have a broad range of chemical composition more than 200 ingredients, including sugars, amino acids, vitamins, minerals, polyphenols and enzymes (Bogdanov et al. 2008). Various studies were conducted to identify the nutritional and non-nutritional constituents

such as enzymes in GH (Khalil et al. 2011) (Moniruzzaman et al. 2013b) (Moniruzzaman et al. 2014). Table 2 showed the summarized chemical composition of GH.

ANTIOXIDANT PROPERTIES OF GH

The term of 'oxidative stress' describes an imbalance between cellular production of reactive oxygen species (ROS); generation of free radicals and the counter acting antioxidant protective activity in a certain organism (Ames et al. 1993; Moylan & Reid 2007). Oxidative stress disorders results from inability of endogenous antioxidants to neutralize the abnormally high level of ROS. The increased level of ROS destroys the complex cellular molecules such as lipids, proteins and DNA (Matough et al. 2012). Cells are naturally equipped with antioxidant defence systems to counter balance free radicals production and protect against oxidative stress through an interacting network of antioxidant enzymes. ROS such as hydroxyl radical (OH·), superoxide anion (O_2·), and hydrogen peroxide (H_2O_2) are naturally generated in the body during normal metabolism. They are neutralized by endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidise (GPx), to prevent oxidative stress (Betteridge 2000). Although, aerobic organisms possess an antioxidant defence system, damage occurs when free radical production exceeds the limit of system's ability and this condition indirectly results in accumulation of H_2O_2 in the cells. Numerous chronic diseases such as cancer, cardiovascular diseases, impairs wound healing and gastrointestinal inflammatory diseases are consequences of oxidative damage. Several modern medicines are introduced in the management of these chronic diseases. The positive and effective outcomes are also achieved from such medicines. However, these medicines offer the increase risk of drug resistance and pronounced side effects. Natural products are believed to have lesser side effects in comparison with synthetic agents. These folk medicines are enriched with several therapeutic properties. They serve as a source of antioxidant and proven to improve the oxidant and anti-oxidant imbalance by reducing the ROS production (Ferreira et al. 2009). GH has been accounted to have high phenolic and non-phenolic content to attenuate oxidative damage. The antioxidant activity of GH is mainly due to the presence of phenolic acids, flavonoids, catalases, peroxides, carotenoids and non-peroxidal components.

Several experimental studies were conducted to confirm the putative anti-oxidative activities of GH on animal models. A recent study observed the protective effect of GH against oxidative stress in young and aged rats. It was revealed that supplementation with GH reduced the DNA damage and plasma malondialdehyde (MDA) level in young rats compared to the control group. GH supplementation also significantly increased the antioxidant cardiac SOD activity and cardiac catalase (CAT) activity in both young and aged rats. Meanwhile, there were no changes in

Table 2: Phytochemical properties of Gelam honey

Chemical compounds	Values	References
Carbohydrate		(Moniruzzaman et al. 2013a); (Hussein et al. 2012)
Total sugar content (%)	64.93 - 69.60	
Reducing sugar (%)	62.17 – 69.16	
Sucrose (%)	0.41 – 2.77	
Protein		
Protein content (g/kg)	3.14	(Moniruzzaman et al. 2013a)
Proline content (mg/kg)	261.33	
Mineral (mg/kg)		(Hussein et al. 2012); (Moniruzzaman et al. 2013b)
Sodium	17.37 – 196.84	
Potassium	23.04 – 1363.40	
Calcium	21.63 – 275. 77	
Iron	2.37 – 142.37	
Magnesium	4.94 – 31.63	
Zinc	4.91 – 29. 23	
Copper	0.29 – 2.21	
Selenium	16.20	
Vitamin (mg/kg)		(Hussein et al. 2012); (Chua et al. 2014); (Chua et al. 2013)
Thiamin	13.85	
Riboflavin	94.21	
Nicotinic acid	355.38	
Panthotenic acid	12.93	
Ascorbic acid	22.90 – 67.36	
Vitamin E (_g/g)	55.59 – 70.70	
Polyphenol		(Moniruzzaman et al. 2013b); (Khalil et al. 2011); (Chua et al. 2014); (Hussein et al. 2011); (Kishore et al. 2011)
Total phenolic content (TPC)	34.30 – 159.74 mg GAE/100g; 8.47 – 71.51 mg RE/100g	
Total flavonoid content (TFC)	1.47 – 32.89 mg RE/100g; 3.24 – 4.30 mg CE/100g; 46.11 QE/100g	(Moniruzzaman et al. 2013a); (Khalil et al. 2011); (Chua et al. 2014); (Hussein et al. 2011); (Kishore et al. 2011)
Phenolic Compounds (_g/100g)		
Gallic acid	859.43–876.80	(Hussein et al. 2011)
Chlorogenic acid	502.77–528.08	
Caffeic acid	428.84–442.01	
p-coumaric acid	301.45–308.31	
Ferulic acid	356.93–381.37	
Ellagic acid	558.78–575.67	
Quercetin	1588.90–1594.30	
Hesperetin	1475.20–1477.78	
Chrysin	1498.60–1504.60	
Enzymes		
Invertase (U/L) †	85.56	(Chua et al. 2013)
Diastase (DN) *	0.57	

erythrocytes superoxide dismutase (SOD) and glutathione peroxidise (GPx) activity in both young and aged group but CAT activity increased in young rats (Sahhugi et al. 2014). A recent study revealed the synergistic effect of GH and ginger on oxidative stress and metabolic profile in streptozotocin-induced diabetic Sprague-Dawley rats. The study claimed that combination of GH and ginger provided a potential antioxidant effect in the diabetic rats. The results showed significant reduction of SOD, CAT activities andreduced MDA level in the diabetic treated rats compared to the normal rats and diabetic control group (Sani et al. 2014). Earlier study also reported that pre-treatment with GH at a dose of 6 mg/ml decreased the DNA damage in gamma-irradiated human diploid fibroblasts (HDFs) (Hussain et al. 2014). Increase gamma-ray exposure resulted decreased cell survival rate in HDFs. However, following treatment with GH at pre- and during-radiation, increased the cell survival rate was observed. The study showed that GH acts as a protective agent against gamma-irradiation in HDFs (Makpol et al. 2012).

In 2013, a new study conducted to utilize an alternate model to observe the anti-oxidative effects of GH on pancreatic hamster cells (HIT-T15) under hyperglycaemic conditions. Pre-treatment of HIT-T15 cellswith GH showed a significant decrease in the production of ROS, glucose-induced lipid peroxidation, a significant increase in insulin content and the viability of cultured cells under hyperglycaemic conditions. The results proved that supplementation with GH to HIT-15 cells give highest cell viability at a concentration of 80 µg/mL and 80 µM, respectively. The cell viability of HIT-15 cells in hyperglycaemic status was significantly increased ($p < 0.05$) following pre-treatment with GH compared to the cells cultured with glucose alone. In addition, the ROS production and MDA level in the both cells under normal and hyperglycaemic condition was inhibited and reduced by the pre-treatment with GH. Pre-treatment with GH extract significantly reduce ($p < 0.05$) F2 isoprostane production. It indicated that GH decreases the damages caused by increased free radicals production in hyperglycaemic state. Moreover, the study also showed that pre-treatment with GH exhibited a significant increase ($p < 0.05$) in insulin content (Batumalaie et al. 2013). From the above findings, it was proven that GH has both anti-oxidant and anti-diabetic properties as it increased the insulin content in hyperglycaemic state.

ANTICANCER PROPERTIES OF GH

Cancer is an abnormal growth of cells derived from a single cell, loses their normal control mechanisms and proliferates continuously by invading adjacent tissues. This is also a process of cellular and organ dysfunction. There are various types of cancer arising from different organs namely; colon, breast, lung and liver. Several studies have been conducted to observe the anti-cancer properties of GH. Combination treatment of GH and ginger extract

showed synergistic effects via increasing the apoptotic rate of HCT 116 colon cancer cells and reducing the $1C_{50}$ of GH required for inhibiting the cells growth. It also showed that co-treatment of GH with Flurouracil (5-FU) has potential anti-tumour effect against colorectal cancer cell by reducing the cell growth compared to the treatment with 5-FU alone (Hakim et al. 2014).

Another study was also conducted to investigate the anti-proliferative effect of GH against HT 29 colon cancer. Comparatively, the result showed that GH was more potent to suppress the growth of colon cancer cells compared to nenas honey, with a lower IC_{50} of 39.0 mg/ml and 85.5 mg/ml, respectively. The results showed decreased in DNA damage and percentage of apoptotic cells in HT29 colon cancer cells treated with GH. It also showed significantly decreased production of prostaglandin E2 (PGE2) levels compared to H202 induced cells without treatment. Thus, the findings suggested that GH is capable to suppress the growth of HT29 colon cancer cells by inducing apoptosis and impeding inflammation (Wen et al. 2012).

In another study, a combination of GH and crude ginger extract was found to have potential chemo preventive effect against HT29 cells. The combined treatment stimulated early apoptosis by up regulation of caspase 9 and IκB genes accompanied by downregulation of the cancer genes. These results highlighted that combination treatment of GH with ginger has an efficient chemo preventive property in managing the cancers (Tahir et al. 2015). However, the study observed on the effect of GH alone on certain cancer cells is still lacking.

ACCELERATE WOUND HEALING PROPERTIES OF GH

Wound healing is a complex biological cascade of cellular and biochemical events consist of 3 phases; inflammation, proliferation and maturation (Vidinsky et al. 2006; Aljady et al. 2000). Despite recent advances in health care, inadequate wound management and development of secondary infections resulting in high morbidity is still an important concern to the public healthcare. Hence, wound management still remains a vital focus of research. Recently, the interest of using alternative therapeutic agents coming from natural sources has increased alarmingly. Honey is one of the ancient and most enduring natural therapeutic agents in the wound management (Salmah et al. 2005; Suguna et al. 1992). An experimental study showed the positive effect of GH against excisional wound on the neck of Sprague-Dawley rats. GH was applied to the wound on day 13 and compared with untreated and saline group. GH treatment accelerated wound contraction compared to commercial gel with less scar formation (Tan et al. 2012).

Another study observed the effect of GH on corneal keratocytes proliferative capacity and phenotypic characterization. The study focused on two different supplemented GH media which were basal media (BM) and basal media with serum (BMS). GH at concentration of 0.0015% in both

media showed the highest proliferative capacity with no morphological changes compared to the control group. The corneal cell supplemented with 0.0015% of GH in the two media showed high density of growth with higher gene expression of aldehyde dehydrogenase (ALDH), quiescent keratocytes, vimentin and fibroblast compared to the control group. In contrast, the alpha smooth muscle actin (α-SMA) expression, was lower in GH treated group compared to the control group. Thus, it is believed that GH at concentration of 0.0015% promoted ex-vivo corneal keratocytes proliferation while retaining desirable phenotype expression. These results showed GH as a potential therapeutic natural agent in improving corneal wound healing (Yusof et al. 2016).

In addition, a group a researchers worked on the wound healing properties of GH and developed the idea of honey hydrogel dressing for the management of wound healing (Mohd Zohdi et al. 2012). It was found out that application of honey hydrogel dressing significantly increased ($p < 0.05$) wound closure rate and the rate of re-pithelialization compared to control hydrogel and OpSite film dressing. Based on the histopathological evidence, it showed that honey hydrogel significantly attenuated inflammatory response ($p < 0.05$) on seventh day of treatment and modulated the proinflammatory cytokines involve in wound healing at molecular level. This study has clearly demonstrated the potential effectiveness of honey hydrogel dressing in accelerating the burn wound healing through the various effects on cellular elements and cytokines involved (Mohd Zohdi et al. 2012).

ANTI-INFLAMMATORY PROPERTIES OF GH

Inflammation is a complex pathological response of the body which is classified as acute and chronic depending on the time and duration of the event (Ferrero-Milliani et al. 2006; Nathan 2002). Inflammatory process takes place in several disease such as cancer, inflammatory bowel disease, central nervous disorder or degenerative disease and autoimmune diseases. Various inflammatory markers such as interleukin 6 (IL-6), IL-12, tumour necrosis factor (TNF) and cyclooxygenase-2 are released during inflammation. These cytokines initiate and implicate the inflammatory process. Nuclear factor kappa B (NF-kB) serves as important regulator for cytokines and growth factors expression in the inflammation (Iwalewa et al. 2007). It was reported that oral administration of GH significantly inhibited the oedema at two and three hrs following carrageenan injection in a one day of pre-treatment model. However, on seventh day pre-treatment rat model, a reduction in oedema started one hr following caarrageenan injection. It showed that a longer duration of GH treatment provided the better outcomes. The treatment with GH showed a significantly decreased in the production of proinflammatory cytokines compared to the control group. A similar effect was observed in indomethacin treated group (NSAID). Plasma was collected to analyse the production of inflammatory mediators

such as NO, PGE2, TNF-α, IL-6, as well asInos and COX-2 following treatment with GH. Interestingly, the production of all the inflammatory mediators were decreased in a dose dependent manner and this suggested that GH is potentially useful for treating inflammatory conditions by reducing the oedema and inflammatory markers (Hussein et al. 2012).

On the other hand, the same group of author had conducted another experiment to investigate the anti-inflammatory mechanism of GH in carrageenan-induced rat paw via NFkB pathway. The rats were supplemented orally with GH (1 or 2 g/kg body weight) at durationof 1 and 7 days. The expression of NFkB (p65 and p50) and ikBa genes in inflamed rat paws were significantly reduced following pre-treatment with GH. The expression of pro-inflammatory mediators such as COX-2 and TNF-alpha were found to be reduced following the treatment with GH in rat paw tissues. It is believed that GH exhibited its inhibitory effect by attenuating NF-kB translocation and inhibiting IkBa degradation, followed by decreasing the inflammatory mediators COX-2 and TNF-α in wound tissues (Hussein et al. 2013).

Instead of oral supplementation, intravenous injections of GH have also proven in giving a potent effect in protecting organ from lethal doses of lipopolysaccharide (LPS). The rabbits were given intravenous injection of 1 mL honey (500 mg/kg in saline). The sample of blood and organs were collected following eight hours of LPS injection and haematological parameters, biochemical tests, histopathology and myeloperoxidase assessment were measured. It was observed that treatment with GH showed protective effects by reducing the neutrophils count and decreasing the myeloperoxidase activity. Less mortality rate was found in the treated group compared to the control group. Thus, honey may exert a potential therapeutic agent in protecting organs against toxicity of LPS (Kassim et al. 2012).

CONCLUSION

To date, researchers give more focus of attention to natural product that has been claimed to have various therapeutic benefits in comparison with the synthetic drugs. Natural honey is well known to have various therapeutic properties such as antioxidant, anticancer, anti-diabetic, anti-inflammatory and improved wound healing effects. Among the honeys, GH is widely used in Malaysia as a traditional medicine. The potential efficacy of GH alone or combined with other herbal extracts draws the attention of many researchers. The positive outcomes were observed following the treatment with GH. Phytochemical properties of GH and its constituents bring forth the desired beneficial effects. This review summarised the evidence-based findings from various studies including experimental and molecular researches. The present review opens the door for the scientists and medical health personnel to carry out the future researches in conjunction with the above therapeutic properties of GH.

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