



# Natural Honey Beneficial to Health, Its Chemical Composition, and Biochemical Activities: A Review

Vesna Karapetkovska-Hristova<sup>a</sup> and Syed Khalid Mustafa<sup>b\*</sup>

<sup>a</sup> Faculty of Biotechnical Sciences, University St. Kliment Ohridski, Bitola, N. Macedonia.

<sup>b</sup> Department of Chemistry, Faculty of Sciences, University of Tabuk, Tabuk, K. S. A.

## Authors' contributions

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

## Article Information

DOI: 10.9734/CJAST/2022/v41i423997

## Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/94161>

**Review Article**

**Received: 21/09/2022**

**Accepted: 24/11/2022**

**Published: 25/11/2022**

## ABSTRACT

Since early antiquity, honey has been utilized worldwide as a balanced meal and in supplementary treatment. It contains over 200 different substances, the majority of which are water, sugars, vitamins, enzymes, amino acids, minerals, and phytochemicals. It has health advantages, including microbial inhibition, healing, and its influence on other disorders. Additionally, it stimulates the immune system and helps immune cells mature. The nutritional value of honey is substantially influenced by the type of plants in the region, the climate, and the production process. Different types of honey were examined by various workers, they found a strong relationship between honey type and HMF, saccharose, and phenolic content, as well as acidity and antioxidant activity. For the level of vitamin C, glucose, and fructose, the combination of variety and manufacturing technique has a substantial influence. The focus of this study is on the biochemical processes and its potential health benefits. However, the precise mechanisms of honey's influence on many illnesses and activities have not yet been fully defined, and more study is necessary to understand their precise contributions.

\*Corresponding author: E-mail: [khalid.mustafa938@gmail.com](mailto:khalid.mustafa938@gmail.com);

**Keywords:** Honey; composition; antioxidants; atherosclerosis; inflammation; immune system.

## ABBREVIATIONS

<i>HMF</i>	: 5-hydroxymethylfurfural
<i>GIT</i>	: Gastrointestinal tract
<i>GERD</i>	: Gastroesophageal reflux ailment
<i>IBS</i>	: Inflammatory bowel syndrome
<i>LDL</i>	: Low-density lipoproteins
<i>HDL</i>	: High-density lipoproteins
<i>MetS</i>	: Metabolic syndromes
<i>TC</i>	: Total cholesterol
<i>NO</i>	: Nitric oxide
<i>ORS</i>	: Oral rehydration answer
<i>DFU</i>	: Diabetic Foot Ulcer
<i>IMS</i>	: Intermembrane space
<i>MOMP</i>	: Mitochondrial outer membrane permeabilization
<i>HCC</i>	: Hepatocellular carcinoma
<i>ROS</i>	: Reactive oxygen species
<i>ER</i>	: Oestrogens receptor
<i>LDH</i>	: Lactate dehydrogenase

## 1. INTRODUCTION

A sweet liquid produced by the honey bees is called honey. Honey is well-known on a global scale since it contains several nutrients that are good for people's health. Egyptians, Greeks, Romans, and Chinese people have all utilized it in the past to treat gastrointestinal injuries and illnesses, such as stomach ulcers. Additionally, it has been employed as a treatment for earaches, sore throats, and coughs [1]. Honey is used internally [2] as a functional meal to offer energy and nutrients to improve critical the body's organs [3] in addition to being utilized externally. This has been done since the start of history. The quality of honey is significantly influenced by its active ingredients, which include organic acids, flavonoids, polyphenols, glucose, and fructose [4]. Due to its useful qualities and nutritional benefits, honey is produced in many nations across the world and is acknowledged as a significant food that provides energy as well as a treatment. Furthermore, the biochemical, physiological, and pharmacological properties of honey are well established.

Apiculture is the study and practice of employing substances from honeybee colonies, such as honey, bee bread, bee venom, bee pollen, propolis, and royal jelly, to maintain, lengthen, and prolong life. Bee products have been rapidly incorporated into both conventional and contemporary medicine in recent years. Due to their effectiveness, bee products are currently

the subject of several research aimed at determining their specific health benefits and pharmacological qualities, which has accelerated the creation of nutraceuticals and functional foods derived from these products. Functional food is defined as food that, when compared to conventionally remediated and nutritive food, can promote improved physiological or psychological health. These outcomes favourably impact great health preservation, wellbeing, and a decrease in chronic disease [5].

Due to its useful qualities and nutritional benefits, honey is produced in many nations across the world and is acknowledged as a significant food that provides energy as well as a treatment. Furthermore, the biochemical, physiological, and pharmacological properties of honey are well established. The biochemical functions, prospective health advantages, and effects of chemical contaminants in honey are the main areas of this review.

## 2. CHEMICAL COMPOSITION OF HONEY

Each floral source has a unique honey composition, but then again seasonal, environmental factors and processing conditions are similarly significant. More than 200 bioactive compounds are present. Some other term for honey is "supersaturated sugar solution." Natural honey has 82.4% of its mass in carbohydrates, 38.5% in fructose, 31% in glucose, 12.9% in other sugars, 17.1% in water, 0.5% in protein, organic acids, multimineral, amino acids, vitamins, phenols, and a plethora of other minor constituents. The ratio of one form of sugar to another is influenced by the source, such as floral pastures, and to a lesser measure by the enzyme invertase, which dissolves normal sugar in grapes and other fruits. This enzyme can be found in the flower where the bees get their nectar, but it is also in the bee itself [6].

Honey contains 76% sugars (34% glucose, 40.5% fructose, 1.9% sucrose) and 5.5% other carbs. While rapeseed honey stands out for having a larger amount of glucose, acacia and chestnut honey are both quite high in fructose. Numerous studies on the fructose/glucose ratio of different honey samples have been undertaken, discovered that samples of honeydew honey from Croatia had slightly more fructose content (32.4%) than glucose (31.0%), whereas samples from Macedonia had more

glucose (36.8%) than fructose (33.6%). According to Ahmed et al. (2014), four samples of honey from various locations in western Algeria range were taken, the glucose and fructose concentration are found from 21.45 to 28.26 g/100 g and 25.20 to 37.64 g/100 g, respectively [7-10]. With a range of 15 to 23%, water is the second-most significant component of honey. The amount of water in honey affects its viscosity, specific weight, maturity, flavour, and crystallization, and is influenced by the weather, the type of bees, the strength of the bee colonies, the humidity and air temperature in the hive, the processing and storage conditions, and the honey's botanical origin.

Due to its hygroscopicity, honey contains a variable amount of water that varies throughout storage according on the air's humidity. Because it affects the stability and resistance of honey to microbiological degradation during storage, it may be claimed that the amount of water in honey plays a significant role in defining both its quality and durability. The probability of fermentation increases with water content [11,12]. Because nectar and pollen are essential components of plants, proteins can be found in honey. Proteins in honey can take the form of simple substances like amino acids or very complicated structures [13]. Protein and amino acid content together make up no more than 0.7% of the total. Nearly all amino acids that are crucial for health are present in honey. Proline, the primary amino acid, is used to gauge how ripe honey is. Normal honeys should include more than 200 mg/kg of proline. Values below 180 mg/kg indicate that the honey has likely been tampered with by the addition of sugar [14].

The components that give honey its scent is known as honey volatiles. Early in the 1960s,

studies on honey volatiles were initiated. The majority of volatile chemicals are most likely derived from plants, although some of them are also likely to be bee-added, according to recent research [15] of volatiles recovered from honey. A large number of chemicals have been identified in various honeys up to this point. Secondary metabolites generated from plants include polyphenols and phenolic acids. In plant systematics, these substances have been employed as chemotaxonomic markers. They have been proposed as potential indicators for identifying the honey's botanical origin [16]. According to reports, dark-coloured honeys contain less flavonoids and more phenolic acid derivatives than light-coloured ones [17].

Mineral compounds are present in honey in various concentrations. In addition to several other components, potassium is the major element in honey (as shown in Table 1). The main mineral element is potassium, which makes up an average of around one third of the total, however there are many different trace elements. Numerous studies have revealed that the trace element composition of honey is mostly influenced by its botanical source. 3.68% or so are in minerals [18]. Minerals in honey increase the value of honey for human consumption even if this portion of the honey is not produced in great quantities. The majority of minerals, including potassium, chlorine, sulphur, calcium, sodium, phosphorus, magnesium, silicon, iron, manganese, and copper, are found in honey [19]. Darker honey varieties contain more minerals than lighter ones when compared to the observed mean value. Of course, a darker species can be found that is less wealthy than some lighter species [20-23].

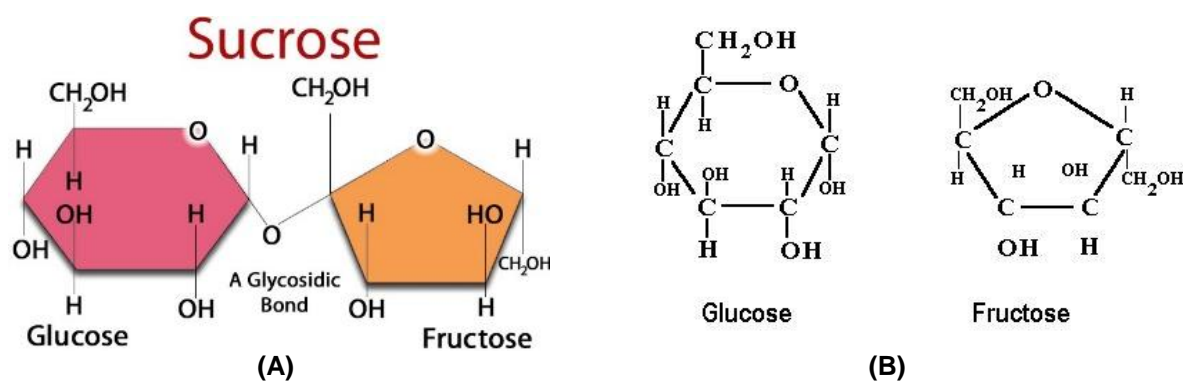


Fig. 1. (A-B)- Structure of sucrose, glucose and fructose

**Table 1. Chemical composition of honey per 100 g**

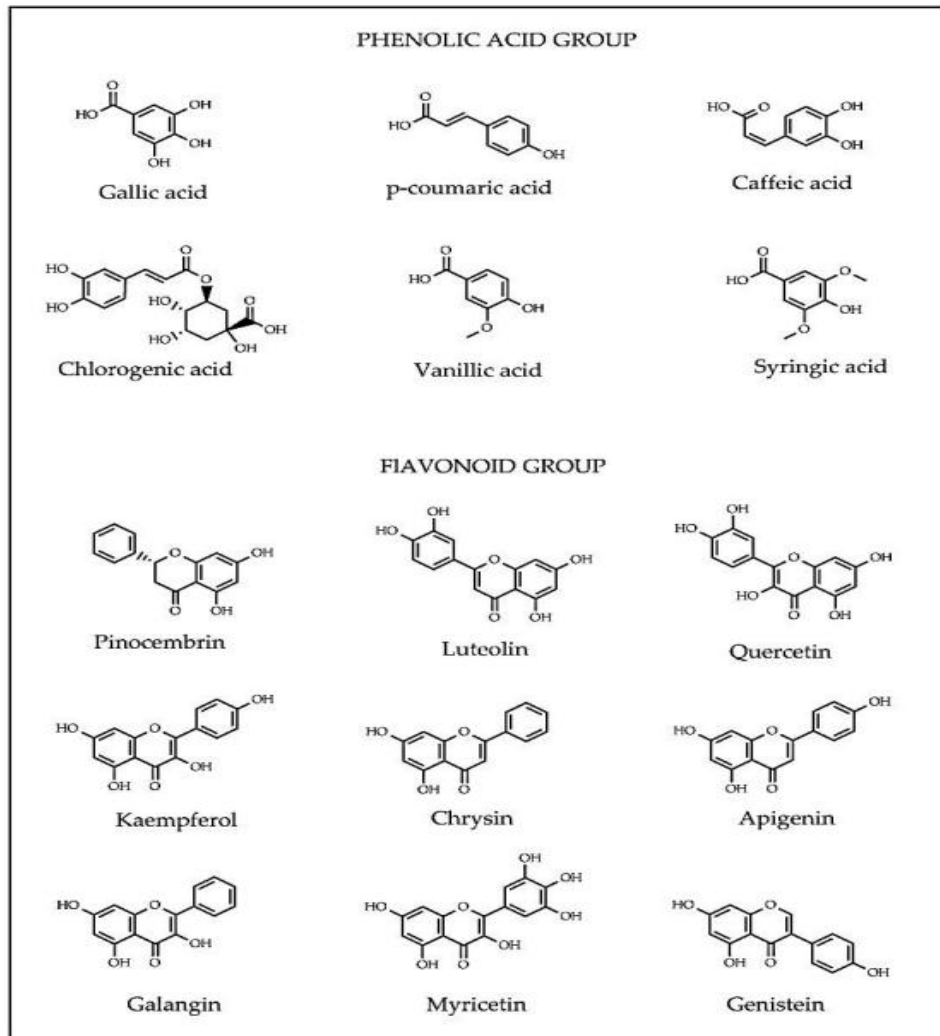
<b>A- Minerals (Average amount present in mg)</b>	
Calcium	4-30
Chlorine	2-20
Zinc	0.05–2.00
Sodium	1.6–17.0
Copper	0.02–0.60
Iron	0.03–4.00
Magnesium	0.7-13
Phosphorous	2 – 15.0
Selenium	0.001–0.003
Potassium	40.0–350.00
<b>B- Proximate (g)</b>	
Fructose	38.2
Glucose	31.3
Sucrose	0.7
Other disaccharides	5.0
Organic acids	0.5
Proteins, amino acids	0.3
<b>C- Vitamins (mg)</b>	
Ascorbic acid	2.2–2.5
Thiamin	0.0–0.01
Riboflavin	0.01–0.02
Niacin	0.1–0.2
Pantothenic acid	0.02–0.11
Pyridoxine (B6)	0.01–0.32

### 3. BIOACTIVE COMPOUNDS IN HONEY

Honey has a lot of beneficial chemicals (Table 1). Bioactive substances include both essential and non-essential elements found in food chains, such as polyphenols and vitamins. These substances are naturally occurring in food and offer advantageous health advantages. Bioactive substances include phenolic compounds. When there are appropriate functional derivatives present, phenols are described as organic compounds having an aromatic ring that is chemically linked to one or more hydrogenated substituents [24]. Honey also contains trace levels of beneficial substances as phenolic acid, flavonoids, and tocopherol [25]. The antioxidant, antibacterial, antiviral, anti-inflammatory, anti-fungal, wound-healing, and cardioprotective effects of phenolic compounds, among others, contribute to the functional qualities of bee products [26]. Phenolic acids, flavonoids, ascorbic acid, proteins, carotenoids, and specific enzymes like glucose oxidase and catalase are among the components of honey that have positive health effects [27].

According to the quantity of vitamins, minerals, antibiotic-rich inhibin, carotenoids, free amino

acids, enzymes, proteins, Maillard reaction products, and phenolic compounds present in honey composition, the non-sugar components, though present in minor quantities, define a specific type of honey and are bioactive [28]. Flavonoids (apigenin, chrysin, galantine, hesperidin, kaempferol, luteolin, myricetin, and quercetin), which are typically heterocyclic ring compounds, are made up of two aromatic rings connected by a carbon bond. Different flavonoid classes, such as flavanols, flavones, flavanones, flavanols, isoflavones, flavanonols, and anthocyanidins, result from variations in the heterocyclic ring compounds. Ring substitutions result in a variety of molecules for each flavonoid family [29]. Phenolic chemicals exert antioxidant capacity (AOC) in a variety of ways, such as metal chelators, free-radical scavengers, or gene modulators of enzymatic and non-enzymatic systems that control cellular redox balance, depending on the molecular structures [30]. A particular phytochemical or mixture of them may be able to identify the location and type of plant from which honey was made [31,32]. Manuka honey, citrus honey, sunflower honey, and lavender honey, among others, all contain methylglyoxal, as do hesperidin, quercetin, and luteolin [33–36].



**Fig. 2. Bio actives common phenolic acid and flavonoid compounds identified in honey**

## 4. HEALTH BENEFITS OF HONEY

### 4.1 Wound Management

Honey has long been used as a remedy for boils, ulcers, burns, insect bites, and skin conditions. The effectiveness of honey as an antibacterial agent and a stimulator of wound regeneration has been supported by scientific research [37]. In the wound matrix, honey encourages the activation of dormant plasminogen, which causes the dynamic production of the proteolytic enzyme. Blood clots contract and fibrin is destroyed by plasmin. It is an enzyme that disintegrates fibrin clots in the wound bed that have adhered dead tissues [38]. Clinical research demonstrating the efficacy, specificity, and sensitivity of honey in wound care suggests that it performs better than traditional and

contemporary wound care dressings [39]. According to certain situations, honey promotes wound healing even in infected wounds that do not react to antiseptics or antibiotics and wounds that have been contaminated with bacteria that are resistant to antibiotics, like methicillin-resistant *Staphylococcus aureus* (MRSA). Additionally, honey promotes the formation of a healthy granulated wound bed and helps with autolytic debridement [40]. Malodor is a characteristic of all serious wounds brought on by *Pepto streptococcus* spp. and *Bacteroides* spp. anaerobic bacterial species [41]. The metabolism of amino acids from putrefied serum and tissue proteins by bacteria results in the production of foul-smelling substances such ammonia, amines, and sulphur. As honey releases a significant amount of glucose, a substrate that bacteria prefer to consume over

amino acids, these molecules are replaced by lactic acids [42]. Fast wound healing, infection clearance, tissue regeneration, reduced inflammation, and improved dressing comfort are some of the therapeutic outcomes seen following honey administration, as well as reduces the tissue adhesion [43].

## 4.2 Paediatric Care

By promoting epithelialization of the affected skin surface, honey also manages skin damage around stomas, such as ileostomy and colostomy [44]. Paediatric dermatitis brought on by frequent use of napkins and diapers, eczema, and psoriasis respond favourably to honey. Patients with psoriasis or atopic dermatitis were studied to see how honey combined with beeswax and olive oil affected their condition. A clinical trial revealed that a honey-based mixture was very well tolerated and produced noticeable improvements. Numerous nitric oxide metabolites found in honey lower the risk of skin infection in psoriasis [45].

## 4.3 Oral Health

Numerous oral conditions, such as halitosis, stomatitis, and periodontal disease, can be helped by honey. Additionally, it has been used to prevent periodontitis, dental plaque, gingivitis, and mouth ulcers. Honey's antibacterial and anti-inflammatory qualities can promote the development of granulation tissue, which in turn helps damaged cells heal [46]. Periodontitis is brought on by the Gram-negative bacterium *Porphyromonas gingivalis*. In addition to preventing periodontal disease, honey has antibacterial effects on this anaerobic bacterium [47]. Stomatitis, an inflammation of the mouth's mucous membranes, can result in ulcers that are clearly visible and extremely painful. Honey is good against stomatitis and quickly penetrates the tissues [48,49]. Bad breath is a symptom of the oral health disorder halitosis. The majority of the oral cavity's odour is brought on by degrading microbial activity [50]. According to a recent study, honey consumption reduces halitosis because of its potent antibacterial properties brought on by its methylglyoxal component [51].

## 4.4 Gastrointestinal (GI) Disease

Enzymes found in natural honey aid in the absorption of compounds like sugars and starches. The sugar molecules in honey are in a shape that makes them simple for the body to absorb. Additionally, honey contains nutrients

like minerals, phytochemicals, and flavonoids that support the body's digestive functions [52]. *Salmonella* spp., *Escherichia coli*, *Shigella* spp., and numerous other Gram-negative species are susceptible to the bactericidal effects of pure honey [53]. Numerous crucially important beneficial microorganisms are found in the gastrointestinal tract (GIT). *Bifidobacteria*, for instance, is one of the microorganisms needed to maintain a healthy GI system. Consuming foods high in probiotics may help the GIT contain more *Bifidobacteria*, according to some research. In the presence of prebiotics, this bacteria's biological processes and growth are significantly improved. Natural honey has a high prebiotic content, according to studies [54]. Honey has been identified as a notable dietary supplement that promotes the proliferation of *Lactobacillus* and *Bifidobacteria* and catalyses their probiotic effectiveness in the GIT, according to certain *in vitro* and *in vivo* experimental studies [55,56]. Prebiotic components in honey such inulin, oligofructose, and oligosaccharides encouraged an increase in *Lactobacillus acidophilus* and *L. plantarum* populations by 10-100 folds under *in vitro* conditions, which was advantageous for the gut microbiota [57].

## 4.5 Dyspepsia, Gastritis, and Peptic Ulcer

In dyspepsia, a persistent condition, the stomach and first portion of the small intestine mostly act improperly. Epigastric discomfort, heartburn, bloating, and nausea are symptoms of the condition. The early sign of a peptic ulcer, which has the potential to develop into cancer, is dyspepsia. The term "gastritis" describes the lining of the stomach wall's irritation and inflammation. Peptic ulcers are painful erosions or open sore ulcers that develop on the lining of the duodenum or stomach. *Helicobacter pylori* (*H. pylori*), the causative agent of peptic ulcers, and gastritis have both been linked to honey [58]. Clinical studies have demonstrated that honey boosted healing effects while reducing stomach acid output. As a result of its antibacterial qualities and preventive effects, honey is consumed as a dietary supplement [59]. Honey's high sugar content and acidic pH are caused by glucose oxidase's conversion of glucose into gluconic acid during the oxidative process. Hydrogen peroxide, which serves as an antibacterial agent, is released by this method. Additionally, fibroblasts and epithelial cell activators are impacted by glucose oxidase, which is necessary for the healing of ulcers brought on by *H. pylori* [43-44].

#### 4.6 Gastroesophageal Reflux disorder

The condition known as gastroesophageal reflux disease (GERD) is a mucosal infection brought on by the abnormal reflux of stomach contents into the esophagus and even the lungs. Heartburn, inflammation, and acid regurgitation are GERD symptoms. By covering the lining of the esophagus and stomach and inhibiting the upward flow of food and gastric fluid, honey consumption aids this condition. Finally reducing the likelihood of acid reflux, honey can further stimulate the sphincter tissues to help with their renewal [60].

#### 4.7 Constipation and Diarrhea

A widespread and diverse condition known as chronic constipation is characterized by uncomfortable feces (irregular stools and difficult stool passage). Straining, difficult stool expulsion, a feeling of incomplete evacuation, hard or lumpy stools, and a longer time to pass stool are all signs of difficult stool passage [61]. A high frequency of bowel motions accompanied by watery stools is referred to as diarrhea. In comparison to traditional antiviral medication, honey has reduced the aetiology and duration of viral diarrhea [62]. In another instance, raw Manuka honey taken on an empty stomach was beneficial in treating persons with inflammatory bowel syndrome (IBS) who were experiencing severe diarrhea or constipation, bloating, and stomach discomfort [63].

#### 4.8. Pharyngitis and Coughs

*Streptococcus* spp. causes pharyngitis, also referred to as sore throat, an acute infection of the oropharynx and nasopharynx [64]. In addition to streptococci, sore throats can also be brought on by viruses, non-streptococcal bacteria, fungi, and irritants such as chemical pollution. Manuka honey's anti-inflammatory, antiviral, and antifungal qualities make it useful for treating sore throats. In addition to relaxing the throat, honey coats the inside lining of the throat and kills any potentially hazardous microorganisms [65,66]. According to a study, honey is more effective than dextromethorphan and diphenhydramine in treating cough brought on by upper respiratory infections [67]. Honey's anti-inflammatory and antibacterial characteristics helped both kids and adults sleep better after consuming it, reducing the severity of recurrent coughs (2.5 ml). According to comparison research on children using various natural items,

honey was discovered to be the most frequently utilized treatment for pneumonia 82.4% of the time [68].

#### 4.9 Metabolic and Cardiovascular Fitness

Natural wild honey has cardioprotective and therapeutic effects against the heart diseases and vasomotor dysfunctions brought on by adrenaline. The total phenolic content of honey and radical scavenging activity have been found to be correlated [69]. Consuming honey significantly decreased the risk factors for cardiovascular and metabolic disorders. In addition to improving lipid profiles and maintaining vascular homeostasis, honey demonstrates cardioprotective benefits [70]. Honey contains flavonoids that enhance coronary vasodilation, reduce platelet clotting potential, limit low-density lipoprotein (LDL) oxidation, raise HDL levels, and enhance endothelial function [71]. Honey has been shown to have beneficial effects on metabolic syndromes (MetS) in a study comparing the metabolic response of honey [72]. Hyperglycaemia, hypertension, abdominal obesity, dyslipidaemia, and heightened susceptibility to diabetes, renal, and heart disorders are all signs of MetS. By suppressing inflammatory and angiogenic pathways, honey's polyphenols lessen atherosclerotic plaques [73]. A clinical trial on hyperlipidaemic individuals revealed that honey reduced total cholesterol (TC) and significantly slowed the rise in plasma glucose levels. A molecule found in honey called nitric oxide (NO) also serves as a cardioprotective agent [74].

#### 4.10 Gastroenteritis

Inflammation of the digestive tract is brought on by gastroenteritis, often known as stomach flu or gastric flu. This syndrome could be brought on by the transfer of infectious organisms through food, water, and person-to-person contact. Dehydration, watery diarrhea, bloating, abdominal cramps, and nausea are all signs of gastroenteritis. This syndrome can be brought on by a variety of infectious organisms, including *Salmonella*, *Shigella*, and *Clostridium* [75]. According to a clinical trial by Abdulrahman from 2010, infantile gastroenteritis can be treated with honey. Due to honey's high sugar content, which accelerates electrolyte and water absorption in the stomach, the study found that patients with gastroenteritis recovered more quickly when honey was used to replace the glucose in

standard electrolyte oral rehydration solution (ORS) [76].

#### 4.11 Diabetic Foot Ulcer (DFU)

Consuming honey is a cheap and successful kind of therapy for DFU. Microbial infections can make DFU more challenging and impede the healing process. Due to their lowered immune response, patients with diabetic peripheral neuropathy may not exhibit symptoms such as pain, oedema, or redness in addition to the infection, further complicating the diagnosis [77]. According to a review, using honey to treat venous ulcers produced effective results with high patient compliance rates [78]. In patients with locally infected wounds, DFU, Charcot foot ulcerations, and complex concomitant disorders that have not responded to hospital therapy, honey is useful in wound management [79]. Additionally, the presence of honey results in high tolerability and minimal harm to the wound bed.

#### 4.12 Liver and Pancreatic sicknesses

Honey aids in detoxification, liver system balance, and pain relief. Oxidative damage is a cause of complications in the hepatic system. Antioxidant properties of honey may have a preventive effect on a damaged liver. According to a study on rats with paracetamol-induced liver damage, honey's antioxidant and hepatoprotective properties significantly reduced liver damage. As it provides sufficient glycogen storage in liver cells, honey, which has a fructose to glucose ratio of 1:1, may assist to produce improved blood sugar levels, which is beneficial for patients with fatty liver disease. Stress hormones are released when the liver doesn't have enough glycogen store, which over time damages glucose metabolism. Insulin resistance is the main cause of fatty liver disease and is brought on by impaired glucose metabolism. Following treatment with Tualang honey, a different study found that blood glucose levels significantly decreased [80-82].

### 5. CANCERS AND ONCOGENESIS

#### 5.1 Colorectal Cancer

A polyp, which often originates on the inner lining of the colon or rectum and develops toward the centre, is where the majority of colorectal malignancies start. While some polyps are not harmful, some will develop into adenomas and may eventually cause cancer. The multiplication

of colon cancer cells was suppressed by the honey, according to a study, that examined the chemo preventive effects of Gelam and Nenas monofloral honeys against colon cancer cell lines. The impact of honey was investigated using colon cancer cells that had been exposed to hydrogen peroxide-induced inflammation. The findings demonstrated that honey reduced inflammatory activity in malignant cells. Another study looked into how crude honey affected the apoptosis of colon cancer cell types. The study verified honey's ability to inhibit cell proliferation in these tissues. Additionally, considerable antiproliferative effect against colon cancer cells was seen at high phenolic concentrations (like those of quercetin and flavonoids). Cell cycle arrest, activation of the mitochondrial pathway, induction of mitochondrial outer membrane permeabilization, induction of apoptosis, modulation of oxidative stress, reduction of inflammation, modulation of insulin signaling, and inhibition of angiogenesis in cancer cells are some of the molecular mechanisms underlying honey's antiproliferative and anticancer effects. Additionally, honey has the capacity to influence cancer-promoting proteins, genes, and cytokines. A number of honey constituents, including chrysin, quercetin, and kaempferol, have been demonstrated to stop the cell cycle in human melanoma, renal, cervical, hepatoma, colon, and oesophageal cancer cell lines at various phases, including G0/G1, G1, and G2/M. The mitochondrial pathway is affected by a number of stimuli, including nutrition, physical stress, oxidative stress, and damage from chemotherapy and radiation, two of the most common cancer therapies. These triggers lead to the release of many proteins from the mitochondria's intermembrane space (IMS), including cytochrome c, which ultimately results in cell death. Honey contains flavonoids that are excellent at triggering the mitochondrial pathway and releasing proteins with cytotoxic potential. The most common anticancer strategy, induction of mitochondrial outer membrane permeabilization (MOMP), resulting in protein leakage from the IMS, which inexorably leads to cell death. Honey reduces the propensity of the mitochondrial membrane to cause MOMP in cancer cell lines. It has also been shown that honey increases the depolarization of the mitochondrial membrane, enhancing the apoptotic impact of tamoxifen. It has been demonstrated that honey's flavonoid components, namely quercetin, cause MOMP and cancer cell death [83-85].



## 5.2 Liver Cancers

Hepatocellular carcinoma is the most typical kind of liver cancer (HCC). In a number of experimental experiments, the anticancer effects of honey on liver cancer cells have been examined. Nitric oxide (NO) levels were significantly reduced and the number of HepG2 cells was significantly reduced in HepG2 cells treated with honey. As a result, the cells' total antioxidant profile improved. Reactive oxygen species (ROS) encourage the survival of HepG2 cells, and sufficient amounts of ROS stimulate cell division and differentiation. This investigation was backed by the fact that the honey treatment reduced the level of NO. As a result, HepG2 cell numbers are decreased and malignant cell growth is inhibited by decreased ROS and increased antioxidant effectiveness. Abdel Aziz et al. also looked at how honey affected HepG2 cell lines in another study. According to the study, honey had distinct concentration-dependent cytotoxic, antimetastatic, and antiangiogenic effects on HepG2 cells [81,83,86].

## 5.3 Breast Cancer

Growth and spread of breast cancer are significantly influenced by imbalances in estrogen signalling pathways and estrogen propagating levels. The estrogen receptor (ER) signalling pathway is frequently targeted by breast cancer treatments. Because of their similar structural makeup to mammalian estrogen, phytoestrogens are a subclass of phytochemicals that can bind to estrogen receptors. The effectiveness of honey in modifying the ER signalling system has been examined in several experimental experiments. In MCF-7 cells, honey has biphasic action, according to another study. When phytoestrogens bind to estrogen receptors, this biphasic action of honey is characterized by an antiestrogenic effect at lower doses and an estrogenic effect at higher concentrations. Additionally, it has been noted that quercetin induces apoptotic effects via ER- and ER-dependent pathways. On the other hand, Tualang honey's cytotoxic effects against human breast cancer cells were shown by increased lactate dehydrogenase (LDH) release, which further showed the cytotoxic characteristics of honey. The study also demonstrated that non-malignant breast cells are not affected by honey's cytotoxic actions; rather, only breast cancer lines are affected. This proves that Tualang honey has a fair chance of success as a

chemotherapeutic drug and exhibits highly specific and selective cytotoxic actions toward breast cancer cell lines [86-94].

## 6. CONCLUSION

The current review focuses on the potential health benefits of honey. It is very rich in bioactive components such as flavonoids, phenolic acids, phenolic compounds, terpenes, and enzymes, and it prevents several diseases and has health-promoting biological functions. Honey has a wide range of benefits and important nutritional properties and functional value. In this way, honey can be developed into a potent non-therapeutic drug. In conclusion, the complexity and variability of honey composition rely on its botanical and geographic origin. Each component has a specific role in nutrition, biology, and technology. They work together to increase honey's overall usefulness, making it special and superior to other natural sweeteners in terms of supplying energy and health advantages.

## ACKNOWLEDGEMENTS

The authors would like to extend their appreciation to the Deanship of Scientific Research at the University of St. Kliment Ohridski, Bitola, Macedonia & the University of Tabuk, Tabuk, K. S. A.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Rao PV, Krishnan KT, Salleh N, Gan SH. Biological and therapeutic effects of honey produced by honey bees and stingless bees: a comparative review. *Revista Brasileira de Farmacognosia*, 2016; 26(5):657–664.
2. Fratellone PM, Tsimis F, Fratellone G. Apitherapy products for medicinal use. *Journal of Alternative and Complementary Medicine*. 2016;22(2):1020–1022.
3. Ajibola A. Physico-chemical and physiological values of honey and its importance as a functional food. *International Journal of Food Sciences and Nutrition*. 2015;2(6)1–9.
4. Alvarez-Suarez JM, Tulipani S, Romandini S, Bertoli E, Battino M. Contribution of

- honey in nutrition and human health: a review. *Mediterranean Journal of Nutrition and Metabolism*. 2010;3(1):15–23.
5. Molan PC. The role of honey in the management of wounds. *Journal of Wound Care*. 1999;8(8): 415–418.
  6. Di Pasquale G, Salignon M, Le Conte Y et al. Influence of pollen nutrition on honey bee health: Do pollen quality and diversity matter? *Plos One*. 2013:e72016 Available:https://doi.org/10.1371/journal.pone.0072016
  7. Janevski S. Prirodno lekovanje so med. Martina komerc, Skopje; 2007.
  8. Vahčić N, Matković D. Kemijske, fizikalne i senzorske značajke meda. URL; 2009. Available:https://dokumen.tips/download/link/kemijske-fizikalne-i-senzorske-karakteristike-meda (Accessed on 01.09.2018)
  9. Primorac Lj, Angelkov B, Mandić LM, Kenjeric D, Nedeljko M, Flanjak I, Pirički PA, Arapceska M. Comparison of the Croatian and Macedonian honeydew honey. *JCEA*. 2009;10(3):263-270.
  10. Ahmed M, Khiati B., Meslem A., Aissat, S. & Djebli, N. Evaluation of Physicochemical and Antioxidant Properties of Raw Honey from Algeria. *J Microbial Biochem Technol*. 2014;S4:006. DOI:10.4172/1948-5948.S4-006
  11. Hatjina F, Costa C, Böhler R et al. Population dynamics of European honey bee genotypes under different environmental conditions. *Journal of Apicultural Research*. 2014;53(233-247):23.
  12. Maughan R. The athlete's diet: Nutritional goals and dietary strategies. *Proceedings of the Nutrition Society*. 2002;61:87-96.
  13. Alvarez-Suarez J, Giampieri F, Battino M. Honey as a source of dietary antioxidants: structures, bioavailability and evidence of protective effects against human chronic diseases. *Current Medicinal Chemistry*. 2013;20:621-638.
  14. Bogdanov S. Honey composition. *The honey book*. 2009;27-36.
  15. Bogdanov S, Martin P. Honey authenticity. *Mitteilungen aus Lebensmitteluntersuchung und Hygiene* . 2002;93:232-254.
  16. Bogdanov S, Ruoff K, Oddo LP. Physicochemical methods for the characterisation of unifloral honeys: A review. *Apidologie*. 2004;35:S4-S17.
  17. Gheldof N, Engeseth NJ. Antioxidant capacity of honeys from various floral sources based on the determination of oxygen radical absorbance capacity and inhibition of in vitro lipoprotein oxidation in human serum samples. *Journal of agricultural and food chemistry* 2002; 50:3050- 3055.
  18. Bogdanov S, Martin P. Honey authenticity. *Mitteilungen aus Lebensmitteluntersuchung und Hygiene*. 2002;93:232-254.
  19. Bogdanov S, Ruoff K, Oddo LP. Physicochemical methods for the characterisation of unifloral honeys: A review. *Apidologie*. 2004;35:S4-S17.
  20. Gheldof N, Engeseth NJ. Antioxidant capacity of honeys from various floral sources based on the determination of oxygen radical absorbance capacity and inhibition of *In vitro* lipoprotein oxidation in human serum samples. *Journal of Agricultural and Food Chemistry*. 2002; 50:3050- 3055.
  21. Mattoon WR. The southern cypress (No. 272). US Department of Agriculture; 1915.
  22. Aili SR, Touchard A, Escoubas P et al. Diversity of peptide toxins from stinging ant venoms. *Toxicon*. 2014;92:166-178.
  23. Ensminger ME, Ensminger AH. *Foods & Nutrition Encyclopedia, Two Volume Set*. CRC press.
  24. Marin F, Martinez M, Uribealago T, Castillo S, M. Frutos. Changes in nutraceutical composition of lemon juices according to different industrial extraction systems. *Food Chemistry*. 2002;78(3) :319–324,.
  25. Küçük M, Kolaylı S, Karaoğlu Ş, Ulusoy E, Baltacı C, Candan F. Biological activities and chemical composition of three honeys of different types from Anatolia. *Food Chemistry*. 2002;100(2):526–534.
  26. Biesalski HK, Dragsted LO, Elmadfa I et al. Bioactive compounds: Definition and assessment of activity. *Nutrition*. 2009; 25(11):1202–1205.
  27. Moniruzzaman M, Khalil M, Sulaiman S, Gan S. Advances in the analytical methods for determining the antioxidant properties of honey: A review. *African Journal of Traditional, Complementary and Alternative Medicines*. 2012;9(1):36–42.
  28. Bogdanov S, Jurendic T, Sieber R, Gallmann P. Honey for nutrition and health: A review. *J. Am. Coll. Nutr*. 2013; 27:677–689. [CrossRef]

29. Balasundram N, Sundram K, Samman S. Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chem.* 2006;99:191–203. [CrossRef]
30. Teixeira J, Gaspar A, Garrido EM, Garrido J, Borges F. Hydroxycinnamic acid antioxidants: An electrochemical overview. *BioMed Res. Int.* 2013;251754. [CrossRef] [PubMed]
31. Hollman PCH, Katan MB. Dietary flavonoids: Intake, health effects and bioavailability. *Food Chem. Toxicol.* 1999; 37:937–942. [CrossRef]
32. Procházková D, Boušová I, Wilhelmová N. Antioxidant and prooxidant properties of flavonoids. *Fitoterapia.* 2011;82:513–523. [CrossRef]
33. Tomas-Barberan FA, Martos I, Ferreres F, Radovic BS, Anklam E. HPLC flavonoid profiles as markers for the botanical origin of European unifloral honeys. *J. Sci. Food Agric.* 2001;81:485–496. [CrossRef]
34. Yao L, Jiang Y, Singanusong R, D’Arcy B, Datta N, Caffin N, Raymont K. Flavonoids in *Australian Melaleuca, Guioa, Lophostemon, Banksia* and *Helianthus* honeys and their potential for floral authentication. *Food Res. Int.* 2004; 37:166–174. [CrossRef]
35. Anklam E. A review of the analytical methods to determine the geographical and botanical origin of honey. *Food Chem.* 1998;63:549–562. [CrossRef]
36. Yao L, Data N, Tomás-Barberán FA, Ferreres F, Martos I, Singanusong R. Flavonoids, phenolic acids and abscisic acid in Australian and New Zealand *Leptospermum* honeys. *Food Chem.* 2003;81:159–168. [CrossRef]
37. Molan PC. The evidence supporting the use of honey as a wound dressing. *The International Journal of Lower Extremity Wounds.* 2006;5(1):40–54,.
38. Esmon CT. Crosstalk between inflammation and thrombosis. *Maturitas.* 2004;47(4):305–314.
39. Vermeulen H, Ubbink D, Goossens A, De Vos R, Legemate D. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. *British Journal of Surgery.* 2005;92(6): 665–672.
40. Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns.* 1998;24(2):157–161.
41. Cooper R, Gray D. The control of wound malodour with honey-based wound dressings and ointments. *Wounds UK, Aberdeen.* 2005;26–32
42. White R, Molan P. A summary of published clinical research on honey in wound management. *Honey: A modern wound management product. Wounds UK, Aberdeen.* 2005;130–143.
43. Molan P. Why honey is effective as a medicine: 2. The scientific explanation of its effects. *Bee World.* 2001;82(1):22–40.
44. Aminu S, Hassan A, Babayo U. Another use of honey. *Tropical Doctor.* 2000;30(4):250–251.
45. Al-Waili NS. Topical application of natural honey, beeswax and olive oil mixture for atopic dermatitis or psoriasis: Partially controlled, single-blinded study. *Complementary Therapies in Medicine.* 2003;11(4):226–234.
46. Anyanechi C, B Saheeb. Honey and wound dehiscence: A study of surgical wounds in the mandibular bed. *Nigerian Journal of Clinical Practice.* 2015; 18(2):251–255.
47. S. Eick, G. Schäfer, J. Kwiecinski, J. Atrott, T. Henle, and W. Pfister, “Honey—a potential agent against *Porphyromonas gingivalis*: An *In vitro* study. *BMC Oral Health.* 2014;14(1)24.
48. Halim DS, Mahanani ES, Saini R, Omar M, Rubiantee bt Ibrahi N, Alam MK. A comparison study on the effectiveness of local honey and salicylate gel for treatment of minor recurrent aphtous stomatitis. *International Medical Journal.* 2013; 20(6):770–772.
49. JJ Song, P. Twumasi-Ankrah, and R. Salcido, “Systematic review and meta-analysis on the use of honey to protect from the effects of radiation-induced oral mucositis. *Advances in Skin & Wound Care.* 2012;25(1):23–28.
50. Sterer N, Rosenberg M. *Breath Odors: Origin, Diagnosis, and Management,* Springer Science & Business Media; 2011.
51. Shiga H, Jo A, Terao K, Nakano M, Oshima T, Maeda N. Decrease of halitosis

- by intake of Manuka honey. General Session of IADR Barcelona. 2010;14.
52. Ajibola A, Chamunorwa JP, Erlwanger KH. Nutraceutical values of natural honey and its contribution to human health and wealth. *Nutrition & Metabolism*. 2012; 9(1):61.
  53. Adebolu T. Effect of natural honey on local isolates of diarrhea-causing bacteria in southwestern Nigeria. *African Journal of Biotechnology*. 2005;4(10):1172.
  54. Abeshu MA, Geleta B. Medicinal uses of honey. *Biology and Medicine*. 2016;8(2):1–7.
  55. S. Kajiwara, H. Gandhi, and Z. Ustunol. Effect of honey on the growth of and acid production by human intestinal *Bifidobacterium* spp.: An *In vitro* comparison with commercial oligosaccharides and inulin. *Journal of Food Protection*®. 2002;65(1):214–218.
  56. T. Shamala, Y. Shri Jyothi, and P. Saibaba. Stimulatory effect of honey on multiplication of lactic acid bacteria under in vitro and in vivo conditions. *Letters in Applied Microbiology*. 2000;30(6):453–455.
  57. Cardarelli HR, Buriti FC, Castro IA, Saad SM. Inulin and oligofructose improve sensory quality and increase the probiotic viable count in potentially synbiotic petit-suisse cheese. *LWT-Food Science and Technology*. 2008;41(6):1037–1046.
  58. Header E, Hashish AEM, ElSawy N, Al-Kushi A, El-Boshy M. Gastroprotective effects of dietary honey against acetylsalicylate induced experimental gastric ulcer in albino rats. *Life Science Journal*. 2016;13:1.
  59. Lychkova A, Kasyanenko V, Puzikov A. Gastroprotective effect of honey and bee pollen. *Experimental & Clinical Gastroenterology*. 2014;9:72.
  60. Abdellah F, Abderrahim LA. 8 honey for gastrointestinal. In *Honey in Traditional and Modern Medicine*. CRC Press, Boca raton, Florida, USA. 2013;159.
  61. Brandt LJ, Prather CM, Quigley EM, Schiller LR, Schoenfeld P, Talley NJ. Systematic review on the management of chronic constipation in North America. *The American Journal of Gastroenterology*. 2005;100:S1:S5–S21.
  62. Andualem B. Synergistic antimicrobial effect of Tenegn honey (*Trigona iridipennis*) and garlic against standard and clinical pathogenic bacterial isolates. *International Journal of Microbiology Research*. 2013;4(1):L16–22.
  63. S Zhang, T Jiao, Y. Chen, N. Gao, L. Zhang, and M. Jiang. Methylglyoxal induces systemic symptoms of irritable bowel syndrome. *Plos One*. 2014; 9(8).Article e105307.
  64. Bessen DE. Tissue tropisms in group a streptococcus: What virulence factors distinguish pharyngitis from impetigo strains? *Current Opinion in Infectious Diseases*. 2016;29(3):295–303.
  65. Gupta RK, S. Stangaciu. Apitherapy: Holistic healing through the honeybee and bee products in countries with poor healthcare system. In *Beekeeping for Poverty Alleviation and Livelihood Security*. Springer. 2014;413–446.
  66. S. Patel, S. Cichello. Manuka honey: An emerging natural food with medicinal use. *Natural Products and Bioprospecting*. 2013;3(4):121–128.
  67. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. *The Journal of Alternative and Complementary Medicine*. 2010;16(7): 787–793.
  68. Memon KN, Shaikh K, Pandhiani BS, Usman G. How do mothers recognize & treat pneumonia in their children at home? A study in union council Jhudo, District Mirpurkhas. *Journal of Liaquat University of Medical & Health Sciences*. 2013; 12(03)208.
  69. Rakha MK, Nabil ZI, Hussein AA. Cardioactive and vasoactive effects of natural wild honey against cardiac malperformance induced by hyperadrenergic activity. *Journal of Medicinal Food*. 2008;11(1):91–98.
  70. R. Afroz, E. Tanvir, N. Karim et al. Sundarban honey confers protection against isoproterenol-induced myocardial infarction in Wistar rats,” *BioMed Research International*. 2016;2016:10 Article ID:6437641.
  71. M. Khalil S. Sulaiman, and L. Boukraa. Antioxidant properties of honey and its role in preventing health disorder,” *The Open Nutraceuticals Journal*. 2010;3(1):6–16.
  72. A. Ajibola. Growth and metabolic response of suckling rats fed with natural honey supplements. *Ommega Internations*. 2016;3(1):1–8.

73. Daleprane JB, da Silva Freitas V, Pacheco A et al. Antiatherogenic and anti-angiogenic activities of polyphenols from propolis. *The Journal of Nutritional Biochemistry*. 2012;23(6): 557–566.
74. Bogdanov S, Jurendic T, Sieber R, P Gallmann. Honey for nutrition and health: A review. *Journal of the American College of Nutrition*. 2008;27(6):677–689.
75. Halligan E, Edgeworth J, Bisnauthsing K et al. Multiplex molecular testing for management of infectious gastroenteritis in a hospital setting: a comparative diagnostic and clinical utility study. *Clinical Microbiology and Infection*. 2014;20(8): O460–O467.
76. Abdulrhman MA, Mekawy MA, Awadalla MM, Mohamed AH. Bee honey added to the oral rehydration solution in treatment of gastroenteritis in infants and children. *Journal of Medicinal Food*. 2010;13(3): L605–609.
77. V. Falanga. Wound healing and its impairment in the diabetic foot. *The Lancet*. 2005;366(9498):1736–1743.
78. C. Dunford and R. Hanano. Acceptability to patients of a honey dressing for non-healing venous leg ulcers. *Journal of Wound Care*. 2004;13(5):193–198.
79. Mohamed H, Salma MA, Al Lenjawi B et al. Enhancing primary healing post ray amputation in a diabetic patient: Efficacy of natural honey. *Journal of Diabetic Foot Complications*. 2014;6(1): 13–18.
80. Wang Y, Li N. Cheng D et al. Antioxidant and hepatoprotective activity of Vitex honey against paracetamol induced liver damage in mice.” *Food & Function*. 2015;6(7):2339–2349.
81. Erejuwa O, Sulaiman S, Wahab M, Sirajudeen K, Salleh MM and Gurtu S. Antioxidant protection of Malaysian Tualang honey in pancreas of normal and streptozotocin-induced diabetic rats. In *Annales d'endocrinologie*. Elsevier. 2010; 291–296.
82. Erejuwa OO, Sulaiman SA, Wahab M, Sirajudeen K, Salleh M, Gurtu S. Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. *International Journal of Biological Sciences*. 2011;7(2):244–252.
83. Erejuwa OO, Sulaiman SA, Wahab MSA. Effects of honey and its mechanisms of action on the development and progression of cancer. *Molecules*. 2011;19 (2):2497–2522,2014.
84. Wen CTP, Hussein SZ, Abdullah S, Karim NA, Makpo SI, Yusof YAM. Gelam and Nenas honeys inhibit proliferation of HT 29 colon cancer cells by inducing DNA damage and apoptosis while suppressing inflammation. *Asian Pacific Journal of Cancer Prevention*. 2012;13(4):1605–1610.
85. S. Jaganathan, M. Mandal. Honey constituents and its apoptotic effect in colon cancer cells. *Journal of Apiprodukt and Apimedical Science*. 2009;1(2):29–36.
86. Abdel Aziz A, Rady H, Amer M, Kiwan H. Effect of some honey bee extracts on the proliferation, proteolytic and gelatinolytic activities of the hepatocellular carcinoma Hepg2 cell line. *Australian Journal of Basic and Applied Science*. 2009;3(3):2754–2769.
87. Germain D. Estrogen carcinogenesis in breast cancer,” *Endocrinology and Metabolism Clinics of North America*. 2011;40(3):473–484.
87. Tsiapara AV, Jaakkola M, Chinou I et al. Bioactivity of Greek honey extracts on breast cancer (MCF-7), prostate cancer (PC-3) and endometrial cancer (Ishikawa) cells: Profile analysis of extracts. *Food Chemistry*. 2009;116(3):702–708.
88. AN. Fauzi MN. Norazmi, Yaacob NS. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. *Food and Chemical Toxicology*. 2011;49(4):871–878.
89. S. Ahmed and N. H. Othman. Honey as a potential natural anticancer agent: a review of its mechanisms. *EvidenceBased Complementary and Alternative Medicine*. 2013;2013:7. Article ID 829070.
90. Syed Khalid Mustafa, Atif Abdul Wahab A. Oyouni, Meshari M.H. Aljohani1 and M. Ayaz Ahmad. Polyphenols more than an Antioxidant: Role and Scope. *J. Pure Appl. Microbiol*. 2020;14(1):47-61.
91. Syed Khalid Mustafa. COVID 19 and human immune function: the chemistry of vitamin - D. *Egyptian Journal of Chemistry*. 2022;65(1)555-564. DOI:10.21608/EJCHEM.2021.82501.4064
92. Biljana Bogdanova Popov, Vesna Karapetkovska -Hristova, Stefce Presilski, Mohhammad Ali Shariati, Stevo Najman.

- Assesment of heavy metals in propolis and soil from Pelagonia region, Republic of Macedonia. Macedonian Journal of Chemistry and Chemical Engineering. 2017; 36(1):23-33.
93. Biljana Bogdanova Popov, Vesna Karapetkovska – Hristova et al. The use of natural bee products as bioindicators of environmental pollution-The Detection of Heavy Metals, Oriental Journal of Chemistry. 2022;38(1):28-36.
94. Daniel Ingo Hefft, Vesna Karapetkovska–Hristova, Naco Jovcevski. Traditional beekeeping Methods of North Macedonia, Bee World; 2022.  
DOI: 10.1080/0005772X.2022.2035062  
Available: <https://www.tandfonline.com/doi/full/10.1080/0005772X.2022.2035062?src=>

© 2022 Karapetkovska-Hristova and Mustafa; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*  
*The peer review history for this paper can be accessed here:*  
<https://www.sdiarticle5.com/review-history/94161>