A review on health benefits and biological action of honey, propolis and royal jelly

Article · August 2021

CITATIONS
13

READS
426

1 author:

Prem Jose Vazhacharickal
University of Agricultural Sciences Bangalore & Mar Augusthinose College, Ramapuram
236 PUBLICATIONS **291** CITATIONS

SEE PROFILE

Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
www.plantsjournal.com
JMPS 2021; 9(5): 01-13

Received: 02-06-2021
Accepted: 10-08-2021

Prem Jose Vazhacharickal
Department of Biotechnology,
Mar Augusthinose College,
Ramapuram, Kerala, India

Corresponding Author:
Prem Jose Vazhacharickal
Department of Biotechnology,
Mar Augusthinose College,
Ramapuram, Kerala, India

A review on health benefits and biological action of honey, propolis and royal jelly

Prem Jose Vazhacharickal

Abstract
There has been an increasing demand for natural products, particularly the bee products in the health conscious society. The art of rearing honey bees in artificial hives is called apiculture and used for collecting various bee products especially honey, bee bread, bee venom, bee pollen, propolis and royal jelly. Honey is considered as the first natural sweetener ever discovered, widely used as a nutritious food supplement and medicinal agent. The quality and taste of honey fluctuate based on the floral preferences, floral sources, climatic conditions and geographic features. The potential health benefits of honey, such as microbial inhibition, wound healing, and its effects on other diseases, are described Honey exhibits antimicrobial, antioxidant, anti-inflammatory, anticancer, antihyperlipidemic, and cardioprotective properties. Due to these properties, it is used in the treatment of eye disorders, gastrointestinal tract diseases, neurological disorders, fertility disorders and wound healing activity. This review paper mainly focus on the biological and therapeutic effects of honey, propolis and royal jelly. These bee products are effective in preventing diseases and promoting good health due to the presence of bioactive compounds such as flavonoids, phenolic acid, phenolic compounds, terpenes, and enzymes. The nutritional properties and functional values of honey, propolis and royal jelly differs widely in accordance with the floral and bee species. These potent apitherapeutic products should be standardized for correct dozes and checked for the allergic effects.

Keywords: antimicrobial activity, health benefits, honey bees, Propolis, royal jelly, anticancer activities.

1. Introduction
Honey bees are reared in artificial hives and collecting various bee products especially honey, bee bread, bee venom, bee pollen, propolis and royal jelly known as apiculture (Pasupuleti *et al*., 2017 [67]; Vazhacharickal and Jose, 2016 [90]; Vazhacharickal and Jose, 2018 [91]). In the health conscious society, honey bee products has gained much attention in traditional and modern medicine (Eteraf-Oskouei and Najafi, 2013 [37]; Meo *et al*., 2017) [60]. Due to the health benefits and pharmacological properties of bee products had created new horizons in the development of nutraceuticals and functional foods (Ruchi, 2017; Kataki *et al*., 2019) [79, 47]. Functional foods promote better physiological or psychological health conditions compared to normal food and leading to healthy condition (Roberfroid, 2000; Roberfroid, 2002) [77, 76].
Honey is used in ancient times across the world as a natural sweetener (Kuropatnicki *et al*., 2018; El-Soud and Helmy, 2012; Saranraj *et al*., 2016) [54, 36, 85]. It is widely used for various applications including clinical and contains 200 distinct chemical compounds (Aparna and Rajalakshmi, 1999; Meo *et al*., 2017) [60]. Honey highly viscous and contains fructose and glucose (80-85%), water (15-17%), ash (0.2%), proteins and amino acids (0.1-0.4%) with trace amounts of enzymes, vitamins and phenolic compounds (Rao *et al*., 2016; Balasooriya *et al*., 2017) [74, 1]. Honey composition varies depending on the plant sources from which bees collect nectar (Fig. 1; Crane and Visscher, 2009; Ball, 2007; Kaškonienė and Venskutonis, 2010) [31, 12, 45]. The universal honey contain similar types of phenolics acids, flavonoids, antioxidants with synergic action of components (Bogdanov *et al*., 2008; Baltrušaitytė *et al*., 2007) [21, 13]. The physical and chemical properties of honey fluctuate based on the floral preferences and sources (Crane and Visscher, 2009; Ball, 2007; Kaškonienė and Venskutonis, 2010) [31, 12, 45]. In addition to floral sources, climatic conditions and geographic features influence physical, chemical and nutritive properties of honey (Kaškonienė and Venskutonis, 2010; Mohammed, 2020; Machado De-Melo *et al*., 2018) [45, 63, 57].
Honey is has been traditionally used by Egyptians, Greeks, Romans and Chinese to heal wounds, gastric ulcers, cough, sore throat, earaches and eye infections (Pasupuleti *et al*., 2017 [67];

Molan, 1999 [64]; El-Soud and Helmy, 2012 [36]; Banerjee *et al*., 2003 [14]; Vazhacharickal *et al*., 2021 [92]). Honey is considered as a functional food to provide energy and nourishment of the vital organs (Bogdanov, 2012; Luchese *et al*., 2017; Pasupuleti *et al*., 2017; Kostić *et al*., 2020) [20, 56, 67, 51]. The components like glucose, fructose, flavonoid, polyphenols and organic acids play a major role in quality and health benefits of honey (Cianciosi *et al*., 2018; Abeshu and Geleta, 2016; da Silva *et al*., 2016) [28, 1, 32]. Honey is recognised world-wide as a medicine, energy source and well known for biological, physiological and pharmacological activities (Saranraj *et al*., 2016; Mijanur Rahman *et al*., 2014; Zulkhairi Amin, 2018) [85, 62, 96].

Propolis is the bee glue refers to the resinous materials collected by bees from different plants (Bankova *et al*., 2000; Burdock, 1998; Bankova *et al*., 2014) [15, 23, 16]. Being derived from Greek, “pro” means defence and “polis” means city or community (Castaldo and Capasso, 2002; Salatino *et al*., 2005) [25, 82]. Propolis is used as a sealant and construction material in the bee hive (Kasote, 2017; Fokt *et al*., 2010; Wagh, 2013) [46, 38, 94]. It also maintain the internal temperature, protect form weathering and prevent invasion of the intruders (Kapare and Sathiyanarayanan, 2020; Simone-Finstrom and Spivak, 2010) [44, 86]. On heating propolis becomes soft and sticky, possess a pleasant smell and maintain an aseptic environment in the bee hive (Pasupuleti *et al*., 2017; Chon *et al*., 2020; Rahim, 2020) [67, 27, 91]. Propolis has antiseptic, anti-inflammatory, antioxidant, antibacterial, antimycotic, antifungal, antiulcer, anticancer, and immunomodulatory properties (Pasupuleti *et al*., 2017 [67]; Martinotti and Ranzato, 2015; Cornara *et al*., 2017; Anjum *et al*., 2019; Rivero-Cruz *et al*., 2020) [58, 30, 7, 75].

Royal jelly is the hypopharyngeal and mandibular secretion of the worker bee which is white in colour and viscous in nature (Buttstedt *et al*., 2018; Chen and Chen, 1995; Ramanathan *et al*., 2018; Miguel and El-Guendouz, 2017) [24, 26, 73, 61]. It is a superfood consumed by the queen bee. On light doses, it is also fed to honey bee larvae in the first 2-3 days of maturation (Buttstedt *et al*., 2018) [24]. Royal jelly is used by the queen throughout her life cycle. Royal jelly is responsible for the longevity of the queen bee and royalactin is the main component (Kunugi and Mohammed Ali, 2019; Kamakura, 2011; Detienne *et al*., 2014) [53, 43, 34]. Royal jelly is widely used as a dietary supplement due to its antibacterial, antitumor, antiallergy, anti-inflammatory, and immunomodulatory effect (Viuda-Martos *et al*., 2008; Ramadan and Al-Ghamdi, 2012; Pavel *et al*., 2011; Khazaei *et al*., 2018) [93, 72, 68, 50].

2. Chemical constituents of honey, propolis and royal jelly

Honey is a supersaturated sugar solution comprising carbohydrates (82.4%), fructose (38.5%), glucose (31%), other sugars (12.9%), water (17.1%) and protein (0.5%) (Rossi and Marrazzo, 2021; Aurongzeb and Azim, 2011; Tappi *et al*., 2019; Pavlova *et al*., 2018) [78, 10, 88, 69]. In addition, honey comprises organic acids, multi-minerals, amino acids, vitamins, phenols, and many other minor compounds especially phenolic acid, flavonoid and alpha tocopherol (Pashte *et al*., 2020; Kumar *et al*., 2010; Cianciosi *et al*., 2018;) [66, 52, 28]. Phenolic acids, flavonoids, ascorbic acid, proteins, carotenods, enzymes like glucose oxidase and catalase enhances the health benefit of honey (Viuda-Martos *et al*., 2008; Khalil *et al*., 2010) [93, 49].

Propolis is the third important bee product after honey and wax which is mainly composed of resins (50%), wax (30%), essential oils (10%), pollen (5%) and other organic compounds (5%) (Kasote, 2017; Viuda-Martos *et al*., 2008; Fokt *et al*., 2010) [46, 93, 38]. The organic components in the propolis includes phenolic compounds, esters, flavonoids, terpenes, beta-steroids, aromatic aldehydes and alcohols (Kapare and Sathiyanarayanan, 2020; Kayaoglu *et al*., 2011) [44, 48]. Propolis has diverse flavonoids especially pinocembrin, acacetin, chrysin, rutin, luteolin, kaempferol, apigenin, myricetin, catechin, naringenin, galangin, and quercetin; two phenolic acids, caffeic acid and cinnamic acid (Dezmirean *et al*., 2021; Benhanifia and Mohamed, 2015) [35, 17]. It is also a source of vitamins especially vitamins B1, B2, B6, C, and E and useful minerals such as magnesium (Mg), calcium (Ca), potassium (K), sodium (Na), copper (Cu), zinc (Zn), manganese (Mn), and iron (Fe) (Ahangari *et al*., 2018; Sun *et al*., 2000) [2, 87]. In addition to this, enzymes like succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase, and acid phosphatase are also present in propolis (Yousef *et al*., 2010; Pasupuleti *et al*., 2017) [67, 95].

The royal jelly has quite unique composition when compared to honey and propolis. Royal jelly consists of water (50%–60%), proteins (18%), carbohydrates (15%), lipids (3%–6%), mineral salts (1.5%), and vitamins (Kunugi and Mohammed Ali, 2019; Kamakura, 2011; Detienne *et al*., 2014) [53, 43, 34]. With around 185 organic compounds, royalactin is the most important protein present in royal jelly (Kunugi and Mohammed Ali, 2019; Kamakura, 2011) [53, 43]. Fatty acid, proteins, adenosine monophosphate (AMP) N1 oxide, adenosine, acetylcholine, polyphenols, and hormones such as testosterone, progesterone, prolactin, estradiol and 10-hydroxy-2-decenoic acid (HAD) are the useful bioactive present in royal jelly (Pasupuleti *et al*., 2017) [67].

3. Bioactive compounds in honey, propolis and royal jelly

Naturally occurring compounds especially polyphenols and vitamins as part of food chains are considered as bioactive (Sagar *et al*., 2018; Biesalski *et al*., 2009) [81, 18]. Phenolic compounds are highly bioactive defined as organic compounds with an aromatic ring that is chemically bonded to one or additional hydrogenated substituents in the presence of corresponding functional derivatives (Delgado *et al*., 2019; Pasupuleti *et al*., 2017) [67]. Flavonoids are the major phenolic compounds present in honey, propolis and royal jelly (Viuda-Martos *et al*., 2008 [93]. Phenolic compounds are responsible for the antioxidant, antimicrobial, antiviral, anti-inflammatory, antifungal, wound healing, and cardioprotective activities of bee products.

Major biological properties of honey includes antioxidant, anti-inflammatory, anti-bacterial, antiviral, anti-ulcer, antihyperlipidemic, antidiabetic and anticancer properties (Viuda-Martos *et al*., 2008; Juszczak *et al*., 2016; Buratti *et al*., 2007) [93, 42, 22]. Honey lowers cardiovascular risks and shows ameliorative effect on plasma glucose, plasma insulin, cholesterol, triglycerides, blood lipids, C-reactive proteins and homocysteine (Al-Waili *et al*., 2013; Bobiş *et al*., 2018) [6, 19]. Honey is proven to improve memory and learning process including enhanced morphology of memory-related brain areas, increased levels of brain-derived neurotrophic factor, reduced brain oxidative stress, increased acetylcholine concentration (Pasupuleti *et al*., 2017; Othman *et al*., 2015; Terzo *et al*., 2020) [67, 65]. The aim of this review is to summarize information on the traditional and clinical uses of honey to augment various biological activities and to treat diseases.

3.1 Chemical constituents of honey

Around 200 compounds are present in honey which mainly comprises of water, sugars, vitamins, enzymes, amino acids and minerals (da Silva *et al*., 2016; Eteraf-Oskouei and Najafi, 2013; Santos-Buelga and González-Paramás, 2017; Ahmad *et al*., 2017) [32, 84, 37]. Sugars dominate 95-99% of honey's dry matter with fructose as the most prevalent (32-38% of total sugar) (Santos-Buelga and González-Paramás, 2017; Ahmad *et al*., 2017) [84]. In addition to fructose and glucose other disaccharides and oligosaccharides including maltose, maltotriose and panose (da Silva *et al*., 2016; Eteraf-Oskouei and Najafi, 2013) [32, 37]. In addition to this various organic acids, minerals and trace elements such as calcium, potassium, sodium, magnesium, phosphorous, sulphur, iron, zinc, copper and manganese (da Silva *et al*., 2016; Eteraf-Oskouei and Najafi, 2013 [37]; Santos-Buelga and González-Paramás, 2017; Ahmad *et al*., 2017) [84, 32].

Various vitamins, including ascorbic acid (Vitamin C), thiamine (Vitamin B1), pantothenic acid (Vitamin B5), riboflavin (Vitamin B2), nicotinic acid (Vitamin B3), pyridoxine (Vitamin B6), biotin (Vitamin B8), folic acid (Vitamin B9) and cyanocobalamin (Vitamin B12), are present (Ciulu *et al*., 2011) [29]. Enzymes and proteins are minor constituents, with the enzymes playing a vital role in various activities, including antimicrobial activity and facilitating calcium absorption (Ariefdjohan *et al*., 2008) [9]. The antioxidant capacity of honey depend on total phenolic compounds and the presence of flavonoids which has an important role in reducing oxidative stress. A variety of flavonoids and terpenoids have been reported in various honeys. In manuka honey, pinocembrin (1), chrysin (2), pinobanksin (3), 8-methoxykaempferol (4), luteolin (5), isorhamnetin (6), galangin (7), kaempferol, sakuranetin (8), quercetin and magniferolic acid (9) and 3ß-hydroxy-24-methylenecycloartan-26-oic acid (10) have been identified (Ahmed and Othman, 2013) [4]. The various physicochemical properties and therapeutic efficacies of honey are depicted in Fig. 2 and Fig. 3.

3.2 Traditional uses of honey

Honey is widely used in traditional medicines across the globe for ages (Jones, 2009; Jahangir *et al*., 2020; Eteraf-Oskouei and Najafi, 2013) [37]. Due to antioxidants present in the honey, it is used as hepatoprotective, cardioprotective agent and prevents gastrointestinal ailments (Rao *et al*., 2016; Hossen *et al*., 2017; Saeed and Jayashankar, 2019) [74]. Ancient Chinese, Egyptians, Greeks, Assyrian, Romans and Indians used honey to treat wounds, and diseases of intestine (Liyanage and Mawatha, 2017; El-Soud and Helmy, 2012) [55, 36]. Honey exerts known antibacterial effects against several microorganisms, including *Escherichia coli*, *Shigella* spp., *Helicobacter pylori* and *Salmonella* spp. (Al Somal *et al*., 1994; McGovern *et al*.,1999) [5, 59]. Honey has anti-inflammatory properties and shows anticancer activities against breast, cervical, postrate and osteosarcoma. Honey is also traditionally used ad diabetic and hypolipidemic agent (Premratanachai and Chanchao, 2014; Ahmed and Othman, 2013; Samarghandian *et al*., 2017; Pasupuleti *et al*., 2017) [70, 4, 83, 67,]. In India, Lotus honey has been traditionally used to treat eye infections and other diseases (Pasupuleti *et al*., 2017) [67].

4. Health benefits of honey

4.1 Wound management

Honey is used as effective agent to treat wounds, insect bites, burns, skin disorders, sores, and boils. The wound healing capacity is attributed as a promoter of wound repair and antimicrobial activity. Honey promote the activation of dormant plasminogen in the wound matrix leading to the expression of proteolytic enzyme plasmin resulting in blood clot retraction and fibrin destructions. Plasmin breaks fibrin clots with attached dead tissues in the wound bed.

The usage of honey in wound care is superior to conventional and modern wound care dressings. Honey stimulates wound healing properties of infected wounds that do not respond to antiseptics or antibiotics. Honey also aids autolytic debridement and accelerates the growth of healthy granulated wound bed.

The application of honey in the case of Malodor infections (*Bacteroides* spp. and *Peptostreptococcus* spp.) replace the release of malodourous compounds (ammonia, amines, and sulfur) by lactic acids. The therapeutic effects observed after honey application include fast healing, wound cleansing, clearance of infection, tissue regeneration, minimized inflammation, and increased comfort during dressing due to lower extent of tissue adhesion (Pasupuleti *et al*., 2017) [67].

4.2 Paediatric care

Honey enhance the epithelialization of skin surfaces and control the skin damage near stomas. Honey is effective in eczema, psoriasis and pediatric dermatitis caused by the usage of napkins and diapers. Honey mixed with bee wax and olive oil significantly improve the psoriasis or atopic dermatitis condition. Various nitric oxide metabolites present in the honey reduce the incidence of skin infection in psoriasis.

4.3 Diabetic Foot Ulcer (DFU)

Honey is considered as a low cost and effective therapy for the treatment of DFU which is often complicated by microbial infections. Honey is used in wound management and is effective among patients with locally infected wounds, DFU and Charcot foot ulcerations.

4.4 Gastrointestinal (GI) disorder:

Consumption of honey facilitate the absorption of molecules especially sugars and starch and aid in the digestive process due to minerals, phytochemicals and flavonoids. Honey has bactericidal properties against pathogenic bacteria and enteropathogens, including *Salmonella* spp., *Escherichia coli*, *Shigella* spp., and many other Gram negative species. The gastrointestinal tract (GIT) contains many important beneficial microbes like Bifidobacteria and consumption of probiotics increase the availability in the GIT. Honey is a good probiotic and dietary supplement that hastens the growth of Lactobacillus, Bifidobacteria and beneficial for the intestinal microbioata.

4.5 Oral health

Many oral diseases especially periodontal disease, stomatitis, and halitosis can be treated with honey. Honey is also popular for the prevention of dental plaque, gingivitis, mouth ulcers, and periodontitis. Honey stimulate the growth of granulation tissue leading to the repair of damaged tissues. Honey has good antimicrobial activity against *Porphyromonas gingivalis* is a Gram-negative bacteria that causes periodontitis. Honey is very effective against mouth ulcers and stomatitis conditions. Due to the presence of methylglyoxal component, the consumption of honey ameliorates halitosis (Pasupuleti *et al*., 2017) [67].

4.6 Pharyngitis and coughs
Pharyngitis, commonly known as sore throat is an acute infection in the oropharynx and nasopharynx induced by *Streptococcus* spp. Honey is very effective in curing sore throat due to its anti-inflammatory, antiviral, and antifungal properties. Honey makes a smooth coat in the inner lining of the throat and destroys harmful microbes and soothing the throat.
Honey is superior to dextromethorphan and diphenhydramine for the treatment of cough induced upper respiratory infections. Due to antioxidant and antimicrobial properties, honey minimize persistent cough, pneumonia and ameliorated sleep.

4.7 Gastroesophageal Reflux disease
Gastroesophageal reflux disease (GERD) is a mucosal infection caused by contents of abnormal gastric reflux into the oesophagus and lungs. Symptoms of GERD include heartburn, inflammation, and acid regurgitation. Intake of honey make a coating on the oesophagus and stomach lining and prevent the upward flow of food and gastric juice. Honey stimulate the regrowth of tissues on the sphincter and reduce acid reflux (Pasupuleti *et al*., 2017) [67].

4.8 Dyspepsia, Gastritis and peptic ulcer
Dyspepsia affect mainly stomach and small intestine and causes epigastric pain, heartburn, bloating and nausea. The preliminary symptom of peptic ulcer is dyspepsia which eventually cause cancer. Gastritis is the irritation and inflammation of the lining of the stomach wall. Honey is a very effective inhibitor for gastritis and the peptic ulcer causing agent, *Helicobacter pylori* (*H. pylori*), and decreased the secretion of gastric acid. The high sugar content and low pH in honey are the results of glucose oxidative conversion to gluconic acid by glucose oxidase and eventually releases hydrogen peroxide. Glucose oxidase also acts on fibroblasts and epithelial cell activators required for the healing of ulcers caused by *H. pylori*.

4.9 Gastroenteritis
Gastroenteritis is known as stomach or gastric flu and leads to the inflammation of the digestive tract. The symptoms of gastroenteritis include dehydration, watery diarrhoea, bloating, abdominal cramps, and nausea. Replacing the glucose in standard electrolyte oral rehydration solution (ORS) with honey reduced the recovery time of patients with gastroenteritis because the high sugar content in honey boosts electrolyte and water reabsorption in the gut.

4.10 Constipation and diarrhoea
Chronic constipation is characterized by intolerable defecation, difficult stool passage characterized by straining, hard or lumpy stool and prolonged time to pass stool. Diarrhoea is defined as a high frequency of bowel movements with watery stool. Honey has minimized the pathogenesis and duration of viral diarrhoea compared to conventional antiviral therapy. Usage of honey on empty stomach prevents diarrhoea, constipation and stomach discomfort in the case of inflammatory bowel syndrome (IBS) (Pasupuleti *et al*., 2017) [67].

4.11 Liver and pancreatic diseases
Honey balances liver systems and neutralize toxins and prevents oxidative damage. The antioxidant and hepatoprotective activity of honey minimized liver damage. Honey reduce the effect of fatty liver as it provide adequate glycogen storage in liver cells. Insufficient glycogen storage in the liver releases stress hormones that impair glucose metabolism over time. Impaired glucose metabolism leads to insulin resistance and is the main factor of fatty liver disease.

4.12 Metabolic and cardiovascular health
Honey act as cardioprotective and therapeutic impacts against epinephrine-induced cardiac disorders and vasomotor dysfunctions. Honey exhibits cardioprotective effects such as vasodilation, balancing vascular homeostasis, and improvements in lipid profile. Flavonoids in honey improves coronary vasodilation, decreases the ability of platelets to form clots, prevents oxidation of low-density lipoproteins (LDL), increases high-density lipoproteins (HDL), and improves endothelial functions.
Honey has a good metabolic response against metabolic syndrome characterized by hyperglycemia, hypertension, abdominal obesity, dyslipidemia, and intensified adaptability towards diabetes, kidney, and heart diseases. Polyphenols in honey reduce atherosclerotic lesions, honey decreased total cholesterol (TC) and noticeably prevented the rise in plasma glucose levels. Nitric oxide (NO) is a metabolite present in honey that also has cardioprotective functions.

4.13 Cancer and oncogenesis
Breast cancer
Imbalance in estrogen signalling pathways and propagating levels of estrogens have important roles in breast cancer growth and propagation. Targeting the estrogen receptor (ER) signalling pathway is the best way to prevent breast cancer. Honey is very efficient in modulating ER signalling pathway and has biphasic activity in MCF-7 cells. Cytotoxic activities of honey in human breast cancer cells were demonstrated by elevated secretion of lactate dehydrogenase (LDH). Honey shows highly specific and selective cytotoxic effects towards breast cancer cell lines and has a good potential as a chemotherapeutic agent.

Liver cancer
The most common type of liver cancer is hepatocellular carcinoma (HCC). Treatment of HepG2 cells with honey minimized the amount of nitric oxide (NO) levels in the cells and decreased the HepG2 cell number greatly. Reduced reactive oxygen species (ROS) and enhanced antioxidant efficacy inhibit cancerous cell proliferation and lowered the number of HepG2 cells.

Colorectal cancer
Most colorectal cancers begin as a polyp, which generally starts on the inner lining of the colon or rectum and grows towards the center. Honey inhibited the proliferation of colon cancer cells. Honey shows significant antiproliferative action against colon cancer cells due to the high phenolic content. The molecular mechanisms resulting in the antiproliferative and anticancer effects of honey include cell cycle arrest, activation of mitochondrial pathway, induction of mitochondrial outer membrane permeabilization, induction of apoptosis, modulation of oxidative stress, reduction of inflammation, modulation of insulin signalling, and inhibition of angiogenesis in cancer cell. Several components of honey such as chrysin, quercetin, and kaempferol have been shown to arrest cell cycle at various phases such as G0/G1, G1, and G2/M in human melanoma, renal, cervical, hepatoma, colon, and esophageal adenocarcinoma cell lines. Flavonoids in

honey are effective in activating the mitochondrial pathway and discharging proteins with potential cytotoxicity. Induction of mitochondrial outer membrane permeabilization (MOMP) is the most prevalent anticancer mechanism. Honey induces MOMP in cancer cell lines by decreasing the mitochondrial membrane potential. Flavonoid constituents of honey, such as quercetin, have been shown to trigger MOMP and lead to cancer cell death.

Apoptosis is a programmed cell death functioning to control cell growth and remove damaged cells from the system. This process also involves MOMP and results in the discharge of IMS proapoptotic proteins such as cytochrome c to activate caspase cascades which results in further disruption of mitochondria. Poly (ADP-ribose) polymerases (PARP) are crucial enzymes involved in apoptosis and DNA repair. Inhibition of the PARP activity makes the cells unable to repair damaged DNA and pass through the G2 and M phases. This events leads to cell cycle arrest, leading to impairment of DNA repair and augmented apoptosis (Pasupuleti *et al*., 2017) [67].

Inhibition of PARP activity by flavonoids in honey is a potential strategy for targeting cancers with defective DNA damage repair. Bcl-2 and Bax are antiapoptotic and proapoptotic proteins, respectively. Bcl-2 is generally overexpressed in cancer. Tumor suppressor p53 is a transcription factor commonly inactivated in various types of tumors. Honey enhances the upregulation of Bax and downregulation of Bcl-2. In addition, it activates caspases 3 and 9 and induces p53, thereby inhibiting cancer.

Low levels of ROS intensify cell proliferation while high levels lead to oxidative damage that contributes to various types of cancer. Regulation of redox homeostasis is vital for normal cell growth and proliferation. Honey is considered as a free radical scavenger and antioxidant, the inhibitory effect of honey on cancer growth and proliferation is due to its ability to modulate oxidative stress. If cancer growth is rapid under high levels of ROS, honey acts as an antioxidant to prevent cancer cell growth by minimizing oxidative stress and scavenging the ROS. Under low ROS levels, honey act as a pro-oxidant and promote cancer cell growth by further generation of ROS and maximizing oxidative stress (Pasupuleti *et al*., 2017) [67].

Inflammation leads to malignancies and cancers. Mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) are the two main pathways responsible for inflammatory response in cells. Activation of MAPK and NF-κB activates proinflammatory genes and generates inflammatory proteins or cytokines. These include cyclooxygenase-2 (COX-2), Creactive protein (CRP), lipoxygenase-2 (LOX-2), interleukins (IL-1β, IL-6), and TNF-α. IL-1β, IL-6, and TNF-α are cytokines that trigger cancer cell proliferation by maintaining the inflammatory phenotype in the tumor microenvironment. Treating and soothing of inflammation aid to suppress the configuration of malignant and benign tumors. Honey reduce tumorigenesis and progression of cancer by reducing the expression of MAPK and NF-κB in cancerous cells. MAPK cascades are the main signalling pathways in the regulation of cell proliferation, survival, and differentiation. For the regulation of immune response, inflammation and oncogenesis, transcription factor NF-κB is essential. Flavonoids in honey induce apoptosis and prevent the release of IL-1β, IL-6, TNF-α, iNOS, and COX-2 (Pasupuleti *et al*., 2017) [67].

Insulin-resistant type 2 diabetes mellitus and obesity enhances tumors, malignancies and cancers. PI3K/Akt is an important pathway in insulin signalling, modulating substrates related to cellular growth, survival and progression. Elevated levels of MAPK, NF-κB, and insulin receptor substrate 1 (IRS-1) along with reduced levels of Akt expression have been actively linked to the development of insulin resistance. The components in the honey especially quercetin revive insulin resistance by enhancing the expression of Akt and on the other hand reducing the expression of IRS, MAPK, and NF-κB. Modulation of insulin signalling by honey leads to anticancer activities. Honey stimulate granulation tissue through its angiogenic effect and shows debridement effects by boosting epithelialization. Honey selectively stimulates angiogenesis in noncancer tissues through the production of hydrogen peroxide while inhibiting angiogenesis in cancer tissues. Honey has antiangiogenic effects, reduces the viability of cancer cells, and lowers the incidence of metastasis by inhibiting the activities of gelatinase and protease. Honey blocks the three main stages of cancer especially initiation, proliferation and progression (Pasupuleti *et al*., 2017) [67].

5. Health benefits of propolis

5.1 Gastrointestinal disorder

Parasitic infection of the GI tract create abdominal pain, diarrhoea, bloating and nausea. Propolis has been reported to have several biological efficacies including anticancer, antioxidant, and anti-inflammatory activities. Propolis is also used clinically to treat viral infections. Propolis inhibits growth and adherence of the trophozoites, promote the detachment of parasitic worms and effective against giardiasis. Propolis also shows antihistaminergic, anti-inflammatory, antiacid, and anti-H. Pylori activities that can be used to treat gastric ulceration.

5.2 Gynecological care

Widespread causes of indicative vaginitis are bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC). The depletion of *Lactobacillus spp*. in the vagina is a distinguished feature of vaginal infections with yeast like fungi and elevated vaginal pH. Diabetes patients are more prone to having vaginal infections caused by *Candida albicans*. Application of 5% aqueous propolis solution resulted in an improvement in vaginal well-being. Propolis has antibiotic, antimycotic and anaesthetic action. Propolis may be used for Recurrent Vulvovaginal Candidiasis (RVVC) and alternative to antibiotics in patients involved with other medications and allergies. Propolis extract solution (PES) also show low toxicity in human cells and can be an alternative treatment for chronic vaginitis. Due to the antifungal properties PES can be used as a antibiofilm material for RVVC to counteract biofilm growth of *C. albicans* and antifungal drug resistance.

5.3 Oral health

The excessive bacterial growth in oral cavity lead to several oral diseases. Propolis restrict bacterial-plaque development periodontitis causing pathogens. Propolis solutions exert a selectively lower cytotoxic action on human gum fibroblasts mouthwash containing propolis have shown effectiveness in healing surgical wounds. Propolis solution is used to disinfect toothbrushes. A 3% ethanolic extract of propolis toothpaste gel showed good potency against gingivitis caused by dental plague. Propolis extracts have also helped cure halitosis; a condition of unpleasant bad breath due to poor oral hygiene. Propolis toothpaste or mouthwash is used for their ability to reduce growth of bacterial plaque and pathogenic microflora

that causes gingivitis and periodontitis.

5.4 Oncological treatment
The propolis has good potential towards human breast cancer treatment due to its induction of apotosis on breast cancer cells and proliferation. Due to the selective toxicity to only tumour cells, it exhibits low or no toxicity towards normal cells. Galangin, a common flavonoid in propolis induce apoptosis and inhibit melanoma cells. Propolis exert a selective cytotoxic action on human lung cancer cells by inducing endoplasmic reticulum stress, apoptosis, and caspase activity and by reducing the mitochondrial membrane potential.

5.5 Dermatological care
Due to its antiallergy, antiinflammation, antimicrobial properties, and promotive action on collagen synthesis, propolis is widely used in skin care products especially creams and ointments. Propolis notably decreased free radical activity in healing the wound beds which supported the repair process and high efficacy in the treatment of acne vulgaris. Propolis also shows positive collagen metabolism in the wound during the healing process by increasing the collagen content of tissues. Propolis is used as an alternative therapy for wound healing to promote wound closure, under human diabetic foot ulcer (DFU).
Fibronectin (FN) is a multifunctional glycoprotein of high molecular weight, which influences the structural stability and functional properties of various organs and tissues. The fibronectin matrix and its accumulation are essential for cell migration, cell proliferation, cell differentiation, cell adhesion, apoptosis, cellular signalling, angiogenesis, collagen biosynthesis, re-epithelialization, clot formation and platelet activity. Fibronectins are very important in the repair mechanisms and granulation of tissues. The accumulation of fibronectin in the extracellular space also modulates the secretion of other repairing components such as collagen type I and type III, tenascin, laminin, and fibrillin.
Propolis enhances wound healing activity due to its components such as flavonoids, phenolic compounds, terpenes and enzymes. It also reduces the activity of free radicals (ROS) in the wound bed favouring the repair process and enhances the collagen metabolism by increasing the amount of type I and type III collagen in tissues. The reduction of ROS and accumulation of collagen aid in balancing the extracellular matrix and generating granulation tissues. Propolis is considered as one of the potential apitherapeutic agent which modify metabolism of fibronectin by developing a fibrous network of extracellular matrix and inhibiting fibronectin disintegration. Quercetin and resveratrol inhibit fibronectin biosynthesis and TGF?-dependent production of fibronectin as well as regulating the expression of fibronectins. The mobility and migration of epithelial cells are dependent on reduced fibronectin content in the extracellular matrix. Propolis has several health benefits in gastrointestinal, gynecological care, oral health, skin care, and oncological treatments.

6. Health benefits of royal jelly
Royal jelly is one of the important honey bee products that have a good potential to treat various human diseases. The royal jelly possess antioxidant, antitumor, antiaging, neurotropic, and anti-inflammatory properties.

6.1 Reproductive health:
Royal jelly is effective in reducing premenstrual syndrome, treatment of urinary problems and promotion of life quality in postmenopausal women. Royal jelly has protective effects against
Oxymetholone-induced reproductive toxin (OXM), which is an active steroid derived from testosterone and induce stermatogenesis. Royal jelly has been traditionally used to treat menopause symptoms by rebalancing the hormonal concentration in the blood, decreasing follicle-stimulating hormones (FSH).
The quality of oocytes decreases with age and the depleted follicle pool hastens hormonal dysregulation. This hormonal dysfunction is responsible for the reduction in ovarian follicle size and oocyte quality. Increased oxidative stress and continuous ovulation causes loss of antioxidants such as catalase, and glutathione S-transferase (GST). These minimizes the size of the follicle pool and oocyte quality. Oxidative stress is controlled by glutathione (GSH), glutathione S-transferase (GST), Glutathione S-Transferase Theta 1 (GSTT1), Bax, and Bcl-2. GSH, GST, and GSTT1 are direct ROS scavengers.
FSH and luteinizing hormone (LH) are the hormones involved in the aging process. The amount of FSH and LH is controlled by estrogen (E2) and inhibin from the ovarian cells. Reduction of the follicle pool size results in an inadequate release of estrogen and inhibin, which results in a rise in FSH levels. The major active component present in royal jelly is 10-hydroxyl-2-decenoic acid. This compound enhances the synthesis of ovulation hormones, maintaining a lower expression of FSH and LH in young ovarian cells. Royal jelly is efficient in preventing depletion of follicle pool and enhances hormonal regulation.

6.2 Neurodegenerative and ageing diseases
Royal jelly stimulates physical and mental functions for the elderly and increases their appetite and weight. Royal jelly exerted neuroprotective effects in Alzheimer’s disease. Royal jelly contains longevity promoting factors and extends the lifespan and improve mental health.

6.3 Wound healing
Royal jelly enhances wound-healing activity, under the effect of royal jelly, human fibroblasts were able to migrate and increase levels of sphingolipids by decreasing the secretion and formation of collagen. It shortens the curing period of desquamated skin lesions. Royal jelly exhibited protective action on human skin against ultraviolet B induced photoaging by promoting collagen production. Royal jelly dressing is also an effective way of treating diabetic foot ulcers due to its vasodilation effects around the affected wound and prevents infections.

7. Conclusions and future prospects
The present review article focusses on the health benefits of bee products especially, honey, propolis and royal jelly. Honey bee products possesses numerous biological, biochemical and physiological activities in animals as well as in humans. The efficacy of these properties depends on the types of phenolic and bioactive compounds present in the honey bee products.
They are effective in preventing diseases and promoting good health due to the presence of bioactive compounds such as flavonoids, phenolic acid, phenolic compounds, terpenes, and enzymes. The nutritional properties and functional values of honey, propolis and royal jelly differs widely. These potent apitherapeutic products should be standardized for correct

dozes and checked for the allergic effects. Further studies are needed to explore the pharmacological activities of these bee products and standardized to have promising health benefits.

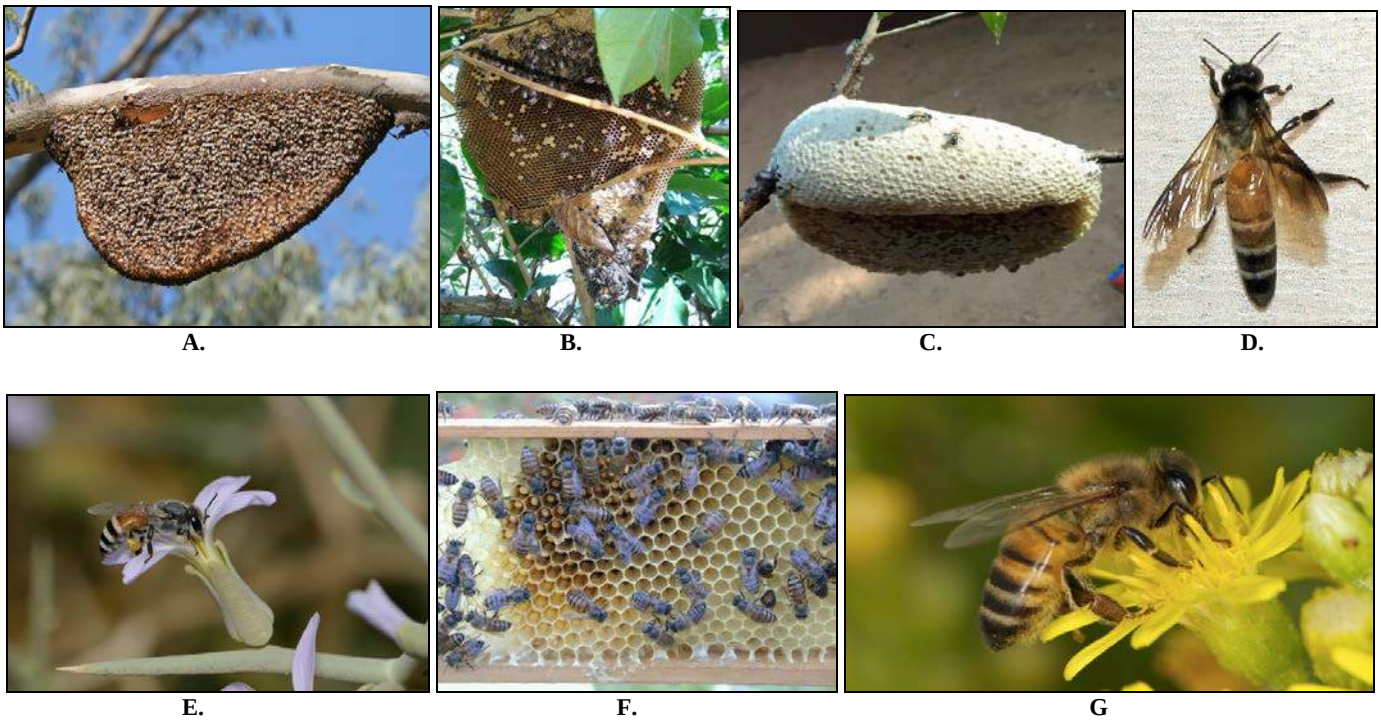

Fig 1: Description of the different honeybees identified in Bengaluru a) Rock bees; *Apis dorsata* b) *Apis florea* comb showing the brood; c) *Apis florea* brood showing honey storage area; d) *Apis dorsata* worker bee e) *Apis florea* worker bee f) *Apis cerena* colony showing brood and stored honey and pollen g) *Apis mellifera* collecting pollen and nectar.

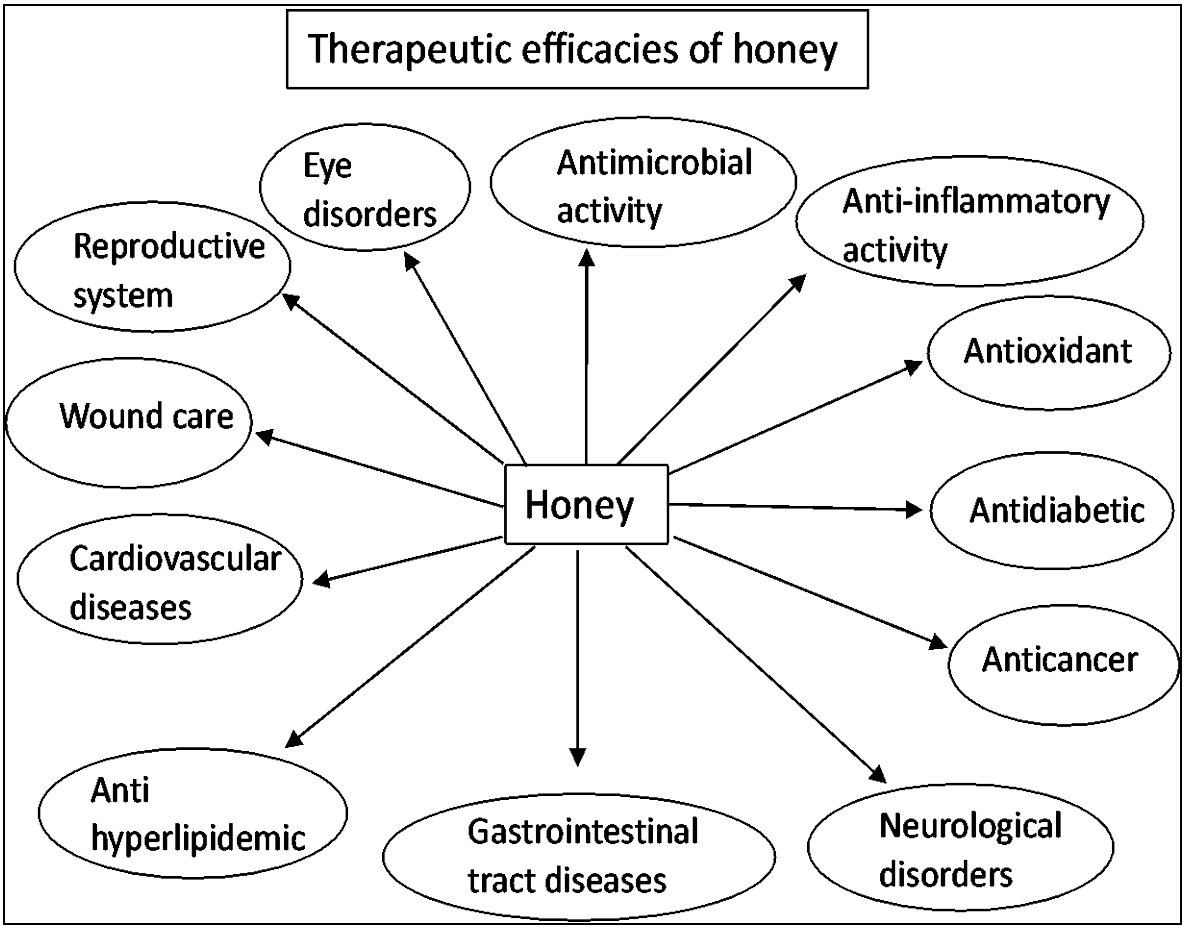

Fig 2: Schematic representation of the therapeutic effects of honey. Adapted from Rao *et al*., 2016 [74]

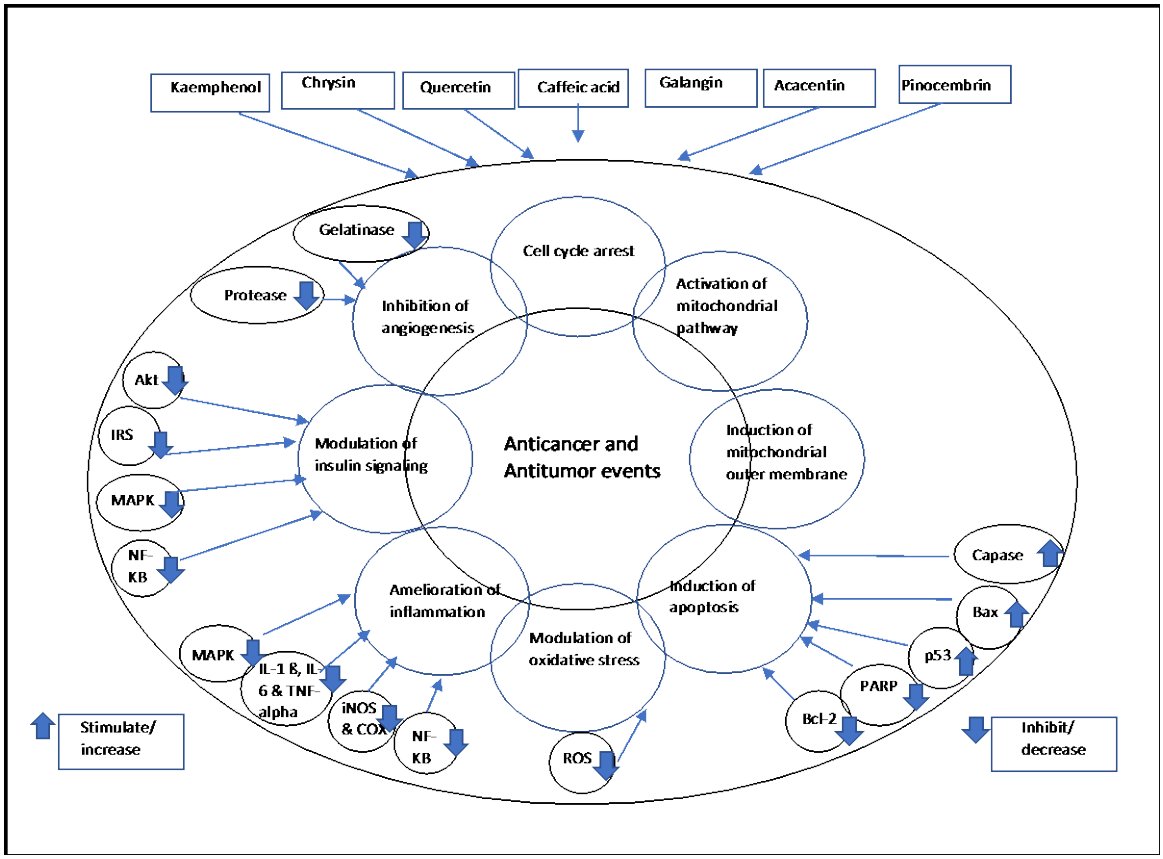

Fig 3: Molecular mechanisms responsible for anticancer and antitumor activities of honey products. IRS—insulin receptor substrate, MAPK—mitogen-activated protein kinase, NF-κB—nuclear factor kappa B, IL-1β—interleukin-1 beta, IL-6—interleukin-6, TNF- α—tumor necrosis factor alpha, iNOS—inducible nitric oxide synthase, COX—cyclooxygenase, ROS—reactive oxygen species, Bcl-2—B- cell lymphoma-2, and PARP—poly (ADP-ribose) polymerases. Adapted from Pasupuleti *et al*., 2017 [67].

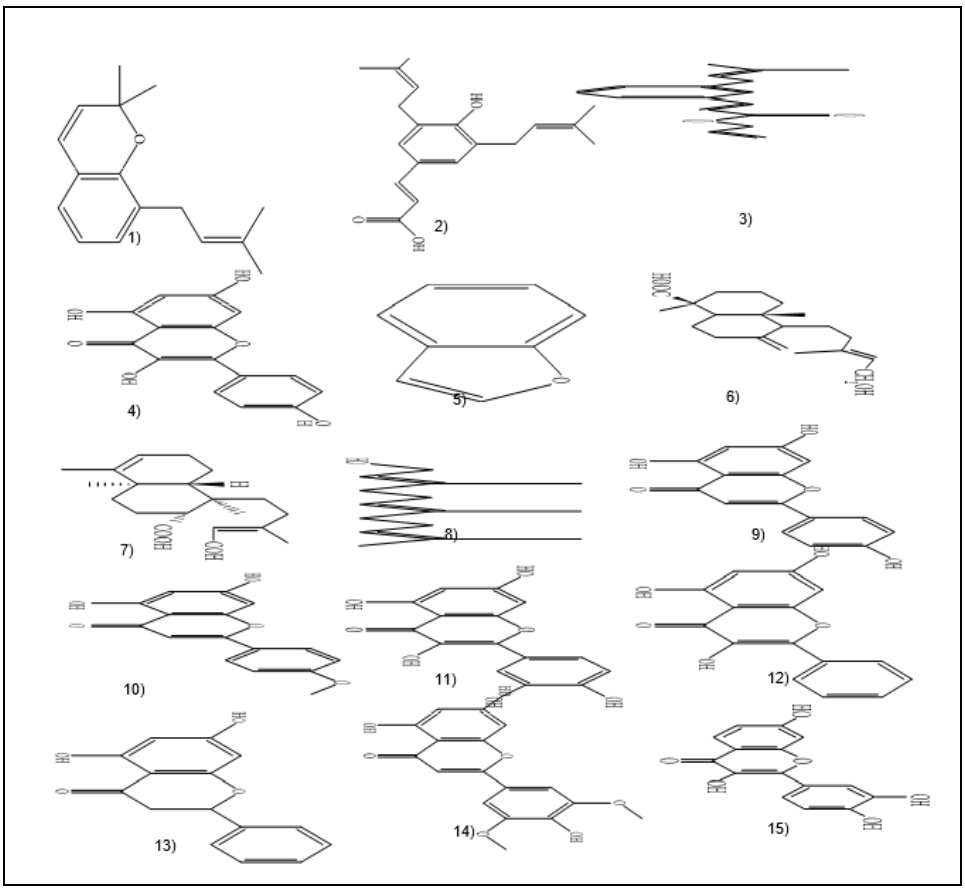

Fig 4: Important bioactive compounds in honey, propolis and royal jelly; 2-dimethyl-8-prenylchromene (1), 4-hydroxy-3, 5-diprenyl cinnamic acid (2), 3-prenyl cinnamic acid allyl ester (3), kaempferide (4), benzofuran (5), isocupressic acid (6), 13C-symphyoreticulic acid (7), farnesol (8), apigenin (9), acacetin (10), quercetin (11), galangin (12), pinocembrin (13), chrysin (14) fisetin (15). Adapted from Rao *et al*., 2016 [74]. Adapted from Pasupuleti *et al*., 2017 [67].

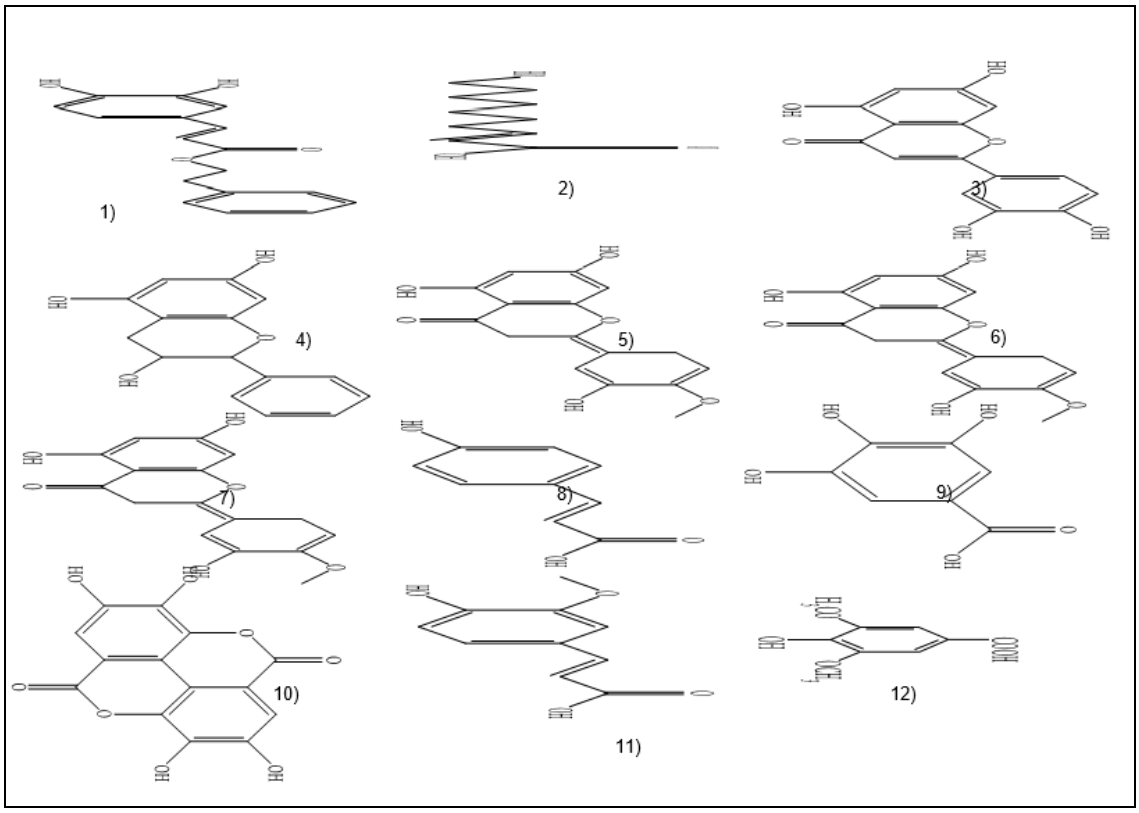

Fig 5: Important bioactive compounds in honey, propolis and royal jelly; caffeic acid (1), 10-hydroxy-2-decenoic acid (2), luteolin (3), pinobanksin (4), hesperetin (5), naringenin (6), genistein (7), p-coumaric acid (8), gallic acid (9), ellagic acid (10), ferulic acid (11), syringic acid (12). Adapted from Pasupuleti *et al*., 2017 [67].

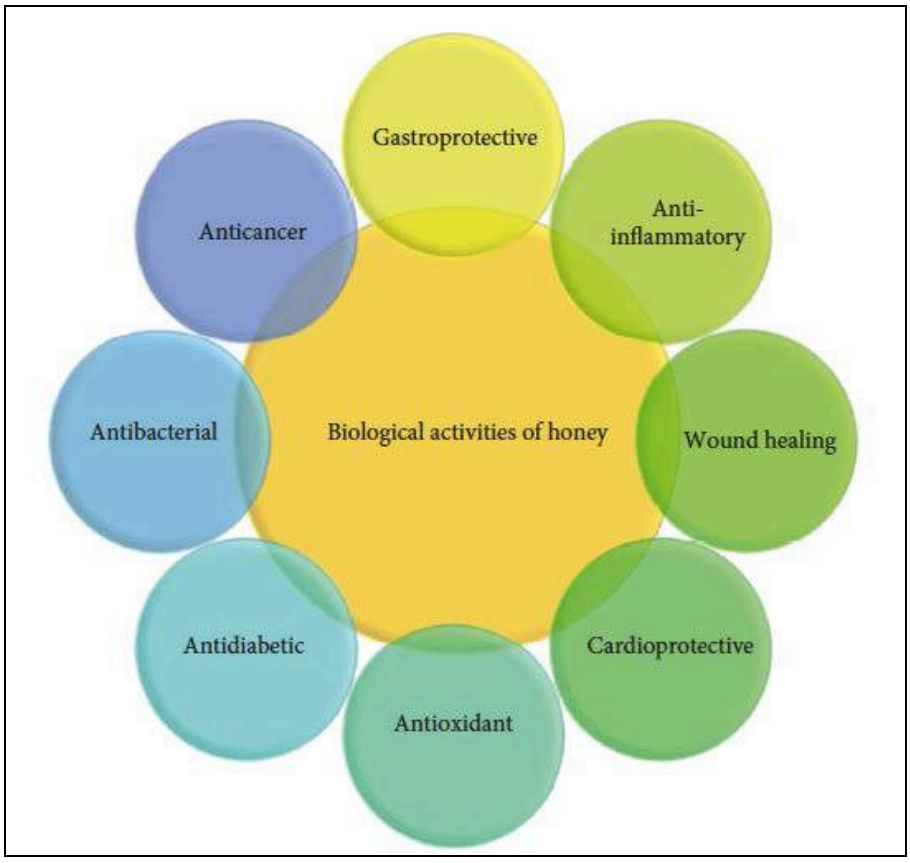

Fig 6: Various types of biological activities of honey products. Adapted from Pasupuleti *et al*., 2017 [67].

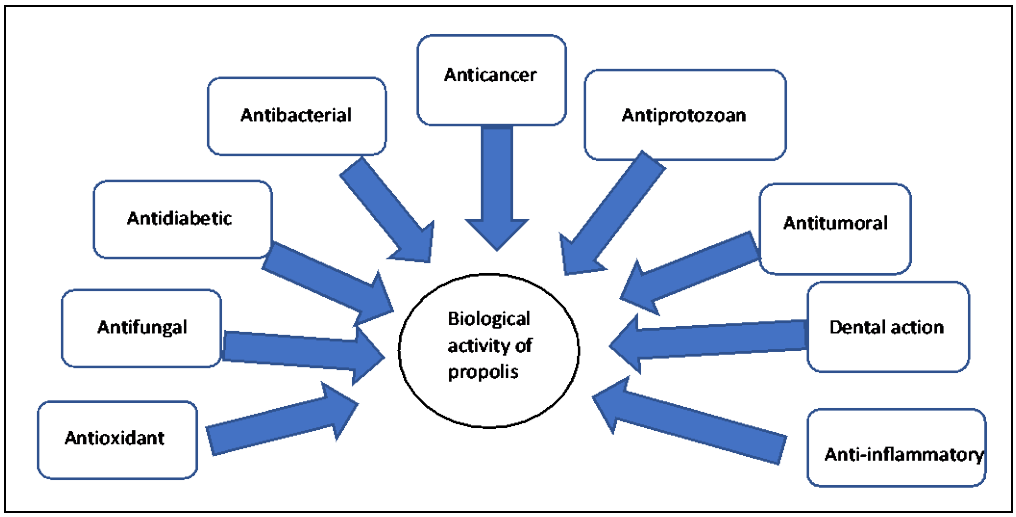

Fig 7: Biological activities of propolis. Adapted from Pasupuleti *et al*., 2017 [67].

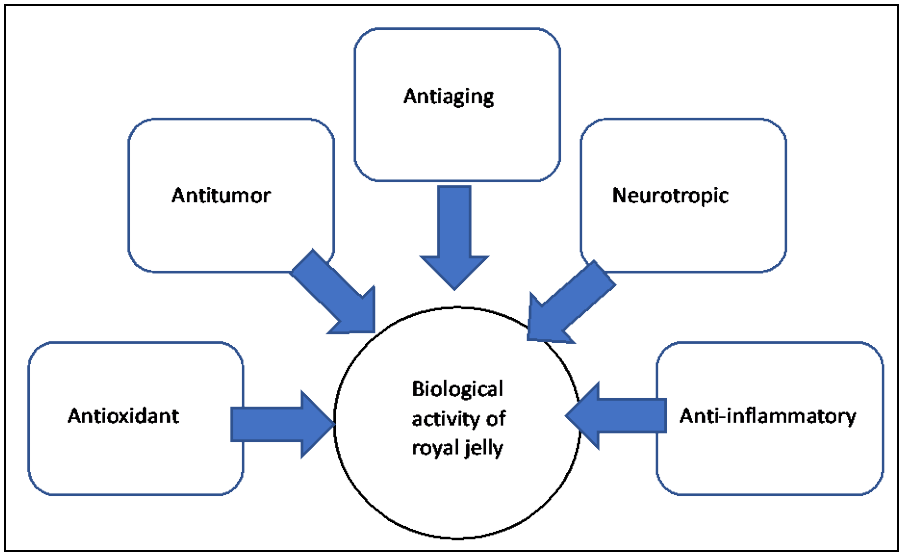

Fig 8: Different types of biological activities of royal jelly. Adapted from Pasupuleti *et al*., 2017 [67].

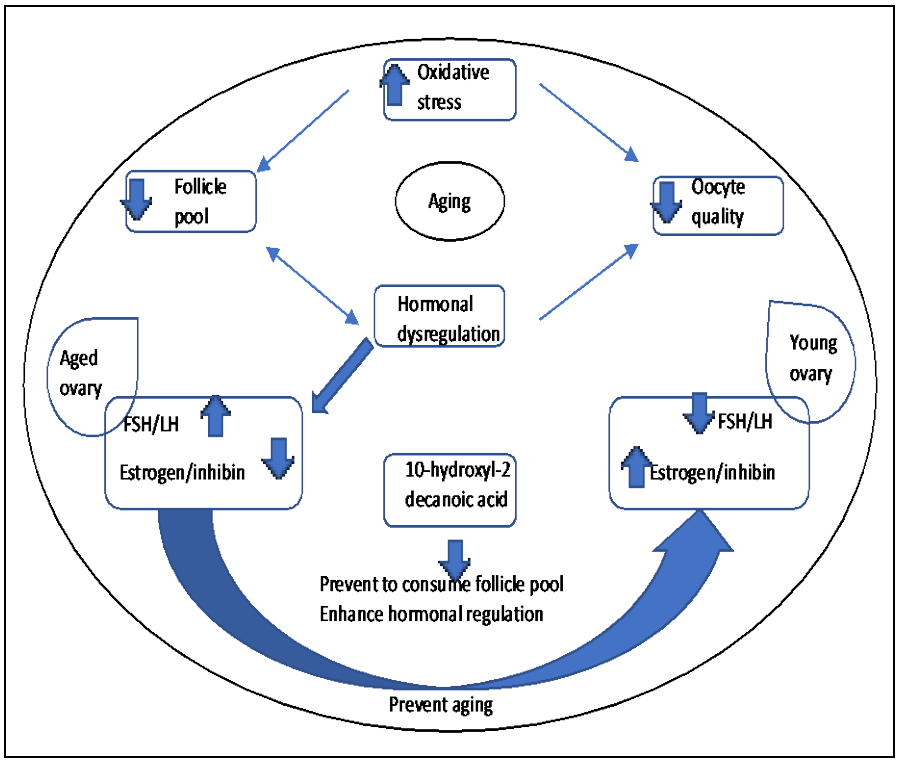

Fig 9: Molecular mechanism responsible for the ageing activity of royal jelly. Adapted from Pasupuleti *et al*., 2017 [67].

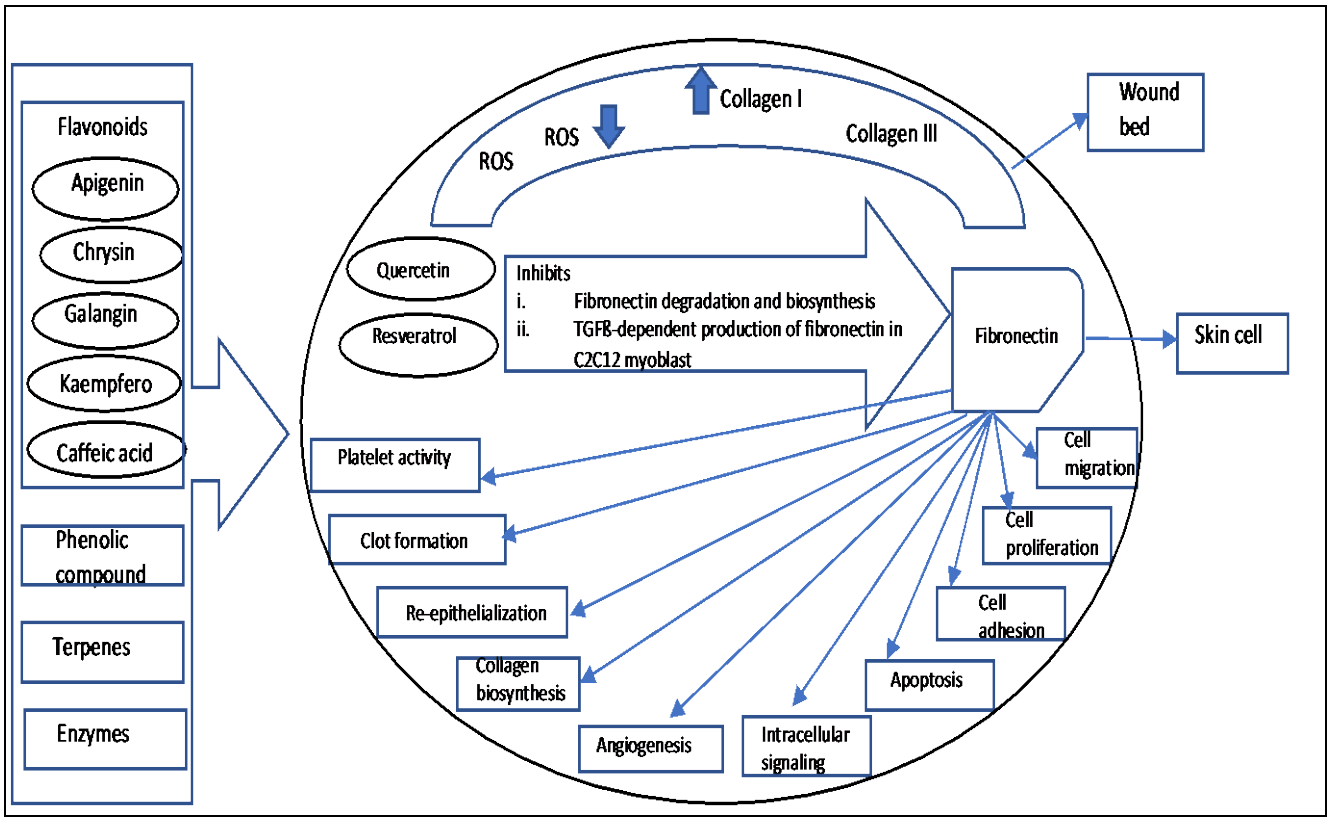

Fig 10: Molecular mechanism targeting wound-healing activity of propolis. Adapted from Pasupuleti *et al*., 2017 [67].

8. Acknowledgment: This outlook study will not be possible by the encouragement and support from Dr. K. B. Umesh, Dr. Andreas Buerkert, Dr. Prasanna Kumar P. S, Dr. Veerabhadrappa Bellundagi, Dr. Hamsa K. R and Dr. Catrin Westphal.

9. Conflicts of interest: The author do not have any conflict of interest.

10. References

1. Abeshu MA, Geleta B. Medicinal uses of honey. Biology and Medicine 2016;8(2): 1.
2. Ahangari Z, Naseri M, Vatandoost F. Propolis: chemical composition and its applications in endodontics. Iranian Endodontic Journal. 2018;13(3):285.
3. Ahmad RS, Hussain MB, Saeed F, Waheed M, Tufail T. Phytochemistry, metabolism, and ethnomedical scenario of honey: A concurrent review. International Journal of Food Properties. 2017;20(1):S254-S269.
4. Ahmed S, Othman NH. Review of the medicinal effects of tualang honey and a comparison with manuka honey. The Malaysian Journal of Medical Sciences: MJMS. 2013;20(3):6.
5. Al Somal N, Coley KE, Molan PC, Hancock BM. Susceptibility of Helicobacter pylori to the antibacterial activity of manuka honey. Journal of the Royal Society of Medicine. 1994;87(1):9.
6. Al-Waili N, Salom K, Al-Ghamdi A, Ansari MJ, Al-Waili A, Al-Waili T. Honey and cardiovascular risk factors, in normal individuals and in patients with diabetes mellitus or dyslipidemia. Journal of Medicinal Food 2013;16(12):1063-1078.
7. Anjum SI, Ullah A, Khan KA, Attaullah M, Khan H, Ali H, Dash CK. Composition and functional properties of propolis (bee glue): A review. Saudi Journal of Biological Sciences 2019;26(7):1695-1703.
8. Aparna AR, Rajalakshmi D. Honey-its characteristics, sensory aspects, and applications. Food Reviews International 1999;15(4):455-471.
9. Ariefdjohan MW, Martin BR, Lachcik PJ, Weaver CM. Acute and chronic effects of honey and its carbohydrate constituents on calcium absorption in rats. Journal of Agricultural and Food Chemistry 2008;56(8):2649-2654.
10. Aurongzeb M, Azim MK. Antimicrobial properties of natural honey: a review of literature. Pak. J. Biochem. Mol. Biol. 2011;44(3):118-124.
11. Balasooriya ER, Jayasinghe CD, Jayawardena UA, Ruwanthika RWD, Mendis de Silva R, Udagama PV. Honey mediated green synthesis of nanoparticles: new era of safe nanotechnology. Journal of Nanomaterials. 2017.
12. Ball DW. The chemical composition of honey. Journal of Chemical Education 2007;84(10):1643.
13. Baltrušaitytė V, Venskutonis PR, Čeksterytė V. Radical scavenging activity of different floral origin honey and beebread phenolic extracts. Food Chemistry. 2007;101(2):502-514
14. Banerjee P, Sahoo KN, Biswas TK, Basu SK, Chatterjee J, Hui AK *et al*. Bees make medicine for mankind 2003.
15. Bankova VS, de Castro SL, Marcucci MC. Propolis: recent advances in chemistry and plant origin. Apidologie. 2000;31(1):3-15.
16. Bankova V, Popova M, Trusheva B. Propolis volatile compounds: chemical diversity and biological activity: a review. Chemistry Central Journal 2014;8(1):1-8.
17. Benhanifia M, Mohamed MW. Phenolics Constituents of Different Types of Propolis and their Antimicrobial Activities. Anti-Infective Agents 2015;13(1):17-27.
18. Biesalski HK, Dragsted LO, Elmadfa I, Grossklaus R, Müller M, Schrenk D *et al*. Bioactive compounds: Definition and assessment of activity. Nutrition. 2009;25(11-12):1202-1205.
19. Bobiş O, Dezmirean DS, Moise AR. Honey and diabetes: the importance of natural simple sugars in diet for

preventing and treating different type of diabetes. Oxidative Medicine and Cellular Longevity 2018.
20. Bogdanov S. Honey as nutrient and functional food. Proteins. 2012;1100:1400-2700.
21. Bogdanov S, Jurendic T, Sieber R, Gallmann P. Honey for nutrition and health: a review. Journal of the American college of Nutrition. 2008;27(6):677-689.
22. Buratti S, Benedetti S, Cosio MS. Evaluation of the antioxidant power of honey, propolis and royal jelly by amperometric flow injection analysis. *Talanta*. 2007;71(3):1387-1392.
23. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food and Chemical Toxicology. 1998;36(4):347-363.
24. Buttstedt A, Mureşan CI, Lilie H, Hause G, Ihling CH, Schulze SH *et al*. How honeybees defy gravity with royal jelly to raise queens. Current Biology 2018;28(7):1095-1100.
25. Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. *Fitoterapia* 2002;73:S1-S6.
26. Chen C, Chen SY. Changes in protein components and storage stability of royal jelly under various conditions. Food Chemistry 1995;54(2):195-200.
27. Chon JW, Seo KH, Oh H, Jeong D, Song KY. Chemical and organoleptic properties of some dairy products supplemented with various concentration of propolis: a preliminary study. Journal of Dairy Science and Biotechnology. 2020;38(2):59-69.
28. Cianciosi D, Forbes-Hernández TY, Afrin S, Gasparrini M, Reboredo-Rodriguez P, Manna PP *et al*. Phenolic compounds in honey and their associated health benefits: A review. Molecules 2018;23(9):2322.
29. Ciulu M, Solinas S, Floris I, Panzanelli A, Pilo MI, Piu PC *et al*. RP-HPLC determination of water-soluble vitamins in honey. *Talanta*. 2011;83(3):924-929.
30. Cornara L, Biagi M, Xiao J, Burlando B. Therapeutic properties of bioactive compounds from different honeybee products. Frontiers in Pharmacology. 2017;8:412.
31. Crane E, Visscher PK. Honey. In Encyclopedia of Insects Academic Press 2009, 459-461.
32. da Silva PM, Gauche C, Gonzaga LV, Costa ACO, Fett R. Honey: Chemical composition, stability and authenticity. Food Chemistry 2016;196:309-323.
33. Delgado AM, Issaoui M, Chammem N. Analysis of main and healthy phenolic compounds in foods. Journal of AOAC International 2019;102(5):1356-1364.
34. Detienne G, De Haes W, Ernst UR, Schoofs L, Temmerman L. Royalactin extends lifespan of *Caenorhabditis elegans* through epidermal growth factor signaling. Experimental Gerontology 2014;60:129-135.
35. Dezmirean DS, Paşca C, Moise AR, Bobiş O. Plant sources responsible for the chemical composition and main bioactive properties of poplar-type propolis. Plants. 2021;10(1):22.
36. El-Soud NHA, Helmy N. Honey between traditional uses and recent medicine. Macedonian Journal of Medical Sciences 2012;5(2):205-214.
37. Eteraf-Oskouei T, Najafi M. Traditional and modern uses of natural honey in human diseases: a review. Iranian Journal of Basic Medical Sciences 2013;16(6): 731.
38. Fokt H, Pereira A, Ferreira AM, Cunha A, Aguiar C. How do bees prevent hive infections? The antimicrobial properties of propolis. Current Research, Technology and Education Topics in Applied Microbiology and Microbial Biotechnology 2010;1:481-493.
39. Hossen MS, Ali MY, Jahurul MHA, Abdel-Daim MM, Gan SH, Khalil MI. Beneficial roles of honey polyphenols against some human degenerative diseases: a review. Pharmacological Reports. 2017;69(6):1194-1205.
40. Jahangir MA, Muheem A, Anand C, Imam SS. Traditional and Modern Applications of Honey: An Insight. In Therapeutic Applications of Honey and its Phytochemicals Springer, Singapore. 2020, 151-169.
41. Jones R. Honey and healing through the ages. Journal of Api Product and Api Medical Science 2009;1(1):1-5.
42. Juszczak L, Gałkowska D, Ostrowska M, Socha R. Antioxidant activity of honey supplemented with bee products. Natural Product Research. 2016;30(12):1436-1439.
43. Kamakura M. Royalactin induces queen differentiation in honeybees. Nature. 2011;473(7348):478-483.
44. Kapare HS, Sathiyanarayanan L. Nutritional and Therapeutic potential of Propolis: A Review. Research Journal of Pharmacy and Technology. 2020;13(7):3545-3549.
45. Kaškonienė V, Venskutonis PR. Floral markers in honey of various botanical and geographic origins: a review. Comprehensive Reviews in Food Science and Food Safety. 2010;9(6):620-634.
46. Kasote DM. Propolis: A neglected product of value in the Indian beekeeping sector. Bee World. 2017;94(3):80-83.
47. Kataki MS, Rajkumari A, Kakoti BB. Functional foods and nutraceuticals: An overview of the clinical outcomes and evidence-based archive. Nanotechnology 2019, 373-400.
48. Kayaoglu G, Ömürlü H, Akca G, Gürel M, Gençay Ö, Sorkun K *et al*. Antibacterial activity of Propolis versus conventional endodontic disinfectants against Enterococcus faecalis in infected dentinal tubules. Journal of Endodontics. 2011;37(3):376-38.
49. Khalil MI, Sulaiman SA, Boukraa L. Antioxidant properties of honey and its role in preventing health disorder. The Open Nutraceuticals Journal. 2010;3(1):1-4
50. Khazaei M, Ansarian A, Ghanbari E. New findings on biological actions and clinical applications of royal jelly: a review, Journal of Dietary Supplements 2018;15(5): 757-775.
51. Kostić AŽ, Milinčić DD, Barać MB, Ali Shariati M, Tešić ŽL, Pešić MB. The application of pollen as a functional food and feed ingredient-the present and perspectives. Biomolecules. 2020;10(1):84-87.
52. Kumar KS, Bhowmik D, Biswajit C, Chandira MR. Medicinal uses and health benefits of honey: an overview. J Chem Pharm Res 2010;2(1):385-395.
53. Kunugi H, Mohammed Ali A. Royal jelly and its components promote healthy aging and longevity: from animal models to humans. International Journal of Molecular Sciences 2019;20(19):4662.
54. Kuropatnicki AK, Kłósek M, Kucharzewski M. Honey as medicine: historical perspectives. Journal of Apicultural Research. 2018;57(1):113-118.
55. Liyanage D, Mawatha B. Health benefits and traditional uses of honey: A review. J. Apith 2017.
56. Luchese RH, Prudêncio ER, Guerra AF. Honey as a functional food. Honey analysis. Intech Open, London 2017, 287-307.
57. Machado De-Melo AA, Almeida-Muradian LBD, Sancho MT, Pascual-Maté A. Composition and properties of *Apis mellifera* honey: A review. Journal of Apicultural

Research. 2018;57(1):5-37.
58. Martinotti S, Ranzato E. Propolis: a new frontier for wound healing?. *Burns & Trauma*. 2015;3(1):1-7.
59. McGovern DP, Abbas SZ, Vivian G, Dalton HR. Manuka honey against Helicobacter pylori. Journal of the Royal Society of Medicine. 1999;92(8):439-439.
60. Meo SA, Al-Asiri SA, Mahesar AL, Ansari MJ. Role of honey in modern medicine. Saudi Journal of Biological Sciences 2017;24(5):975-978.
61. Miguel MG, El-Guendouz S. Volatile compounds of royal jelly. In Bee Products-Chemical and Biological Properties Springer, Cham. 2017, 191-197.
62. Mijanur Rahman M, Gan SH, Khalil M. Neurological effects of honey: current and future prospects. Evidence Based Complementary and Alternative Medicine 2014.
63. Mohammed MEA. Factors Affecting the Physicochemical Properties and Chemical Composition of Bee's Honey. Food Reviews International. 2020, 1-12.
64. Molan PC. Why honey is effective as a medicine. 1. Its use in modern medicine. Bee World. 1999;80(2):80-92.
65. Othman Z, Zakaria R, Hussain NHN, Hassan A, Shafin N, Al-Rahbi B *et al*. Potential role of honey in learning and memory. Medical Sciences. 2015;3(2):3-15.
66. Pashte VV, Pashte SV, Said PP. Nutraceutical properties of natural honey to fight health issues: A comprehensive review. Journal of Pharmacognosy and Phytochemistry. 2020;9(5):234-242.
67. Pasupuleti VR, Sammugam L, Ramesh N, Gan SH. Honey, propolis, and royal jelly: a comprehensive review of their biological actions and health benefits. *Oxidative* Medicine and Cellular Longevity 2017.
68. Pavel CI, Mărghitaş LA, Bobiş O, Dezmirean DS, Şapcaliu A, Radoi I *et al*. Biological activities of royal jelly-review. Scientific Papers Animal Science and Biotechnologies 2011;44(2):108-118.
69. Pavlova T, Stamatovska V, Kalevska T, Dimov I, Nakov G. Quality characteristics of honey: a review. Proceedings of University of Ruse. 2018;57(10.2):32-37.
70. Premratanachai P, Chanchao C. Review of the anticancer activities of bee products. Asian Pacific Journal of Tropical Biomedicine 2014;4(5):337-344.
71. Rahim MKA. Structural and biochemical characterization of bees propolis (Doctoral dissertation, Pusat Pengajian Sains Perubatan, Universiti Sains Malaysia) 2020.
72. Ramadan MF, Al-Ghamdi A. Bioactive compounds and health-promoting properties of royal jelly: A review. Journal of Functional Foods 2012;4(1):39-52.
73. Ramanathan ANKG, Nair AJ, Sugunan VS. A review on Royal Jelly proteins and peptides. Journal of Functional Foods. 2018;44:255-264.
74. 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;26:657-664.
75. Rivero-Cruz JF, Granados-Pineda J, Pedraza-Chaverri J, Pérez-Rojas JM, Kumar-Passari A, Diaz-Ruiz G *et al*. Phytochemical constituents, antioxidant, cytotoxic, and antimicrobial activities of the ethanolic extract of Mexican brown propolis. *Antioxidants*. 2020;9(1):70-75.
76. Roberfroid M. Functional food concept and its application to prebiotics. Digestive and Liver Disease. 2002;34:S105-S110.
77. Roberfroid MB. Defining functional foods. Functional Foods 2000;9:9-27.
78. Rossi M, Marrazzo P. The potential of honeybee products for biomaterial applications. Biomimetics 2021;6(1):6-8.
79. Ruchi S. Role of nutraceuticals in health care: A review. International Journal of Green Pharmacy (IJGP). 2017;11(03):1-6.
80. Saeed MA, Jayashankar M. Therapeutic properties of honey. Journal of Global Biosciences. 2019;8(12):6600-6615.
81. Sagar NA, Pareek S, Sharma S, Yahia EM, Lobo MG. Fruit and vegetable waste: Bioactive compounds, their extraction, and possible utilization. Comprehensive Reviews in Food Science and Food Safety, 2018;17(3):512-531.
82. Salatino A, Teixeira ÉW, Negri G. Origin and chemical variation of Brazilian propolis. Evidence Based Complementary and Alternative Medicine. 2005;2(1):33-38.
83. Samarghandian S, Farkhondeh T, Samini F. Honey and health: A review of recent clinical research. Pharmacognosy Research. 2017;9(2):121-126.
84. Santos-Buelga C, González-Paramás AM. Chemical composition of honey. In Bee Products-Chemical and Biological Properties Springer, Cham. 2017, 43-82.
85. Saranraj P, Sivasakthi S, Feliciano GD. Pharmacology of Honey: A Review. Advances in Biological Research. 2016;10(4):271-289.
86. Simone-Finstrom M, Spivak M. Propolis and bee health: the natural history and significance of resin use by honey bees. Apidologie. 2010;41(3):295-311.
87. Sun F, Hayami S, Haruna S, Ogiri Y, Tanaka K, Yamada Y *et al*. *In vivo* antioxidative activity of propolis evaluated by the interaction with vitamins C and E and the level of lipid hydroperoxides in rats. Journal of Agricultural and Food Chemistry 2000;48(5):1462-1465.
88. Tappi S, Laghi L, Dettori A, Piana L, Ragni L, Rocculi P. Investigation of water state during induced crystallization of honey. Food Chemistry 2019;294:260-266.
89. Terzo S, Mulè F, Amato A. Honey and obesity-related dysfunctions: A summary on health benefits. The Journal of Nutritional Biochemistry 2020;82:108401.
90. Vazhacharickal PJ, Jose S. Nesting behavior and habitats of the stingless bee Trigona iridipennis Smith in Kerala. Amzon Publishers, NY, USA 2016.
91. Vazhacharickal PJ, Jose S. Stingless bees culture (Meliponiculture) in Kerala: hand book for farmers. Amazon Publishers, NY, USA 2018.
92. Vazhacharickal PJ, Jagadish KS, Eswarappa G. Biological and Therapeutic Effects of Honey: An Overview. Int. J. Curr. Res. Aca. Rev. 2021;9(3):23-30.
93. Viuda-Martos M, Ruiz-Navajas Y, Fernández-López J, Pérez-Álvarez JA. Functional properties of honey, propolis, and royal jelly. Journal of Food Science 2008;73(9):R117-R124.
94. Wagh VD. Propolis: a wonder bees product and its pharmacological potentials. Advances in Pharmacological Sciences, 2013.
95. Yousef MI, Kamel KI, Hassan MS, El-Morsy AM. Protective role of propolis against reproductive toxicity of triphenyltin in male rabbits. Food and Chemical Toxicology. 2010;48(7):1846-1852.
96. Zulkhairi Amin FA, Sabri S, Mohammad SM, Ismail M, Chan KW, Ismail N *et al*. Therapeutic properties of stingless bee honey in comparison with European bee honey. Advances in Pharmacological Sciences 2018.