



Potential of apitherapy in the management of cardiovascular diseases

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ABSTRACT

Apitherapy has been used as an adjunctive medical practice in several countries, and bee products or apitherapeutic agents are being consistently utilized for millennia by humanity to treat and prevent an assortment of illnesses. This review sought to explore the relationship between apitherapy and scientific research and experimental trials utilizing bee products within the domain of cardiology. Numerous studies conducted *in vivo* along with *in vitro* indicate that these products may have potential benefits in the prevention and management of cardiovascular diseases (CVDs). This concise review of research reveals new facets of the biological activities of many bee products: honey, propolis, bee venom, pollen, royal jelly, beeswax, and bee bread, as naturally occurring and intriguing remedies for common CVDs. There are undoubtedly some intriguing mechanisms in bee products that aid in the treatment and prevention of CVDs. Future research with larger sample sizes and improved techniques is needed to validate the relationship between bee products and CVD risk factors. Conclusively, bee products seem to have the potential to lower cardiovascular disease risk factors; however, more research is required to fully grasp these benefits. Even if our knowledge of bee products has greatly expanded, it is still crucial to fully utilize its potential, standardize its use, and share the results in academic and non-academic settings to further investigate its potential in the area of cardiology.

1. Introduction

For centuries, various civilizations have utilized the bioactive constituents found in bee products, for instance, honey, propolis, royal jelly, bee pollen, beeswax, and bee venom, to treat a multitude of ailments [1]. Recent years have seen an increase in interest in the study of natural products for the prevention or treatment of various illnesses, additionally, showing more interest in apitherapy and bee products [2,3]. Apitherapy is the utilization of bees or their products for prophylactic or therapeutic purposes to control the progression or prevention of diseases. These days, many countries include apitherapy in their complementary and integrative medicine due to their nutritional value, thus the expenditure on different bee products such as dietary supplements and nutraceuticals has been on the rise trend-wise [4]. Recent research on bee products' pharmacological activity has revealed numerous biological properties, with studies and clinical trials showing their potential for treating diseases and maintaining health balance [5–7]. Besides being used in the food and cosmetics industry, the pharmaceutical industry is paying attention to apitherapy in search of new drugs [8]. The cardioprotective potential of different bee products and how they exert cardioprotective effects have been outlined in this review.

1.1. Apitherapy

The traditional knowledge from certain civilizations that aims to reinstate body homeostasis is the foundation of apitherapy. It is a sub-part of alternative medicine, and while allopathic medicine has plenty of advantages, apitherapy takes a more holistic approach to healing [9]. Api-pharmacopeia involves the utilization of hive products either by themselves or in conjunction with medicinal plants or their derivatives, as well as experimental protocols that incorporate api-medicine and bees [10] to treat illnesses like infections, arthritis, multiple sclerosis, and their symptoms; along with ache and injuries like abrasion and burns [9]. Apitherapy has currently been demonstrated to be a scientifically supported practice. The chemical makeup and, thus, the therapeutic effects of various bee products can differ based on the origin [11, 12]. The soil, climate, harvesting and storage techniques, and botanic sources all affect the quality of products used in apitherapy. Despite the widespread belief that natural products are risk-free, information regarding negative effects or interactions between bee products and common medications is still little known. More emphasis on the magnitude of strengthening communication between apitherapists, beekeepers, researchers, nutritionists, doctors, and consumers is

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extensively required.

1.2. Historical context of integration of bee products

Bee interactions must've prevailed before the emergence of *Homo sapiens*, and possibly that mankind and bees have been related since our predecessors' earliest times [13]. Non-human primates used tools to access the hives, as evidenced by ethnographic records and rock art [14]. Rupestri paintings, hieroglyphics, archaeological excavations, and temples are the places where the history of bees and their products can be found [14,15]. When people started their beekeeping and creating artificial cavities where the bees could reside and produce their goods that is when beekeeping history was first recorded. The earliest humans consumed honey, bee larvae, and pollen [14]. Due to bee stings, early men acquired the skill of locating hives and were the first to undergo apitherapy. According to numerous religious texts, such as the Bible, the Quran, and the Vedas, honey has been put to use for millennia [16]. The empirical study of apitherapy has its origins in ancient Egypt and China. Greeks and Romans utilized products from bees for medicinal purposes. Numerous nations, including Nigeria, Germany, Switzerland, Romania, Lithuania, Slovenia, Bulgaria, and others, have long recognized it [17, 18]. Not everyone has access to the current state of medical science and technology everywhere. Apitherapy is a simple yet efficient way to address medical issues in humans, and it demands development as well as advancement. A bee colony is similar to a "pharmaceutical factory" [15].

2. Cardiovascular diseases and their prevalence

Cardiovascular disease (CVD) is a term used to refer to the range of diseases which affect the heart and blood vessels. These include hypertension (high blood pressure); coronary heart disease (heart attack); cerebrovascular disease (stroke); heart failure; and other heart diseases. Because of the constantly shifting environment in the cardiology field which requires, timely and accurate CVD statistics are crucial in monitoring and prognosis of the disease development [19]. Among other illnesses, cardiovascular disease is the major cause of death globally. Recent data indicates that cardiovascular illnesses claimed the lives of almost 17.9 million people worldwide or 32 % of all deaths. The impact of cardiovascular disease on public health systems may be reduced to a minimum by implementing preventative and early identification approaches and utilizing medical technological developments [20]. Cardiovascular diseases include coronary heart disease, cerebrovascular diseases, rheumatic heart disease, peripheral arterial disease, congenital heart diseases deep vein thrombosis, and pulmonary embolism. Some of the heart disease risk factors and stroke are an unhealthy diet, absence of exercise, tobacco use, and alcohol abuse. Obesity, elevated blood pressure, glucose level, and lipid level can all result from these factors. It is advised to discontinue smoking, cut back on salt, increase intake of fruits and vegetables, get regular exercise, and stay away from alcohol in order to lower the possible chances of cardiovascular disease. CVDs may also be triggered by factors like stress, poverty, aging populations, urbanization, globalization, and genetics. Although in many countries health systems need major investment and reorientation to effectively manage CVDs, Eliminating the incidence of CVDs requires including strategies for managing CVDs in global healthcare plans. Besides, The following basic medications ought to be accessible: statins, beta-blockers, aspirin, angiotensin-converting enzyme inhibitors, etc, treating CVDs requires certain surgical procedures. These consist of balloon angioplasty, artificial heart operations, valve replacement and repair, and coronary artery bypass surgery. To treat certain cardiovascular diseases, medical devices such as pacemakers, prosthetic valves, and patches that seal heart holes are also essential. Natural products, sourced from plants and other natural reservoirs, hold promise in preventing and managing CVDs. These nature-derived bioactive compounds offer potential avenues for maintaining heart health. Prior and current research on bee

products as an approach to the treatment and management of cardiovascular diseases are under investigation.

3. Apiculture products with their cardiovascular potential

Before delving into the usefulness of apitherapy for the management of cardiac conditions, it is essential to comprehend the bee products' relevance to the bees and hive. Royal jelly, beeswax, and venom are all chemically produced by bees themselves; on the other hand, honey, propolis, pollen, and bee bread are products of bees' modification of plant material [1]. Fig. 1 summarizes core compounds available in various bee products for their different types of bioactivities.

3.1. Honey

Bees gather and process the secretions from living plant parts, such as floral nectar, to create honey. After being placed, it is dried out, stored, and allowed to develop in the honeycomb. One of the primary energy sources for bees is honey, which is mostly composed of carbohydrates with trace amounts of proteins, minerals, vitamins, and organic acids [21,22]. Understanding the composition of honey based on the phyto-geography of its production ensures its authenticity and enhances the taste of food. To distinguish between different honey origins, multivariate statistical analysis is necessary due to the vast amount of data related to honey [22]. Since ancient times, people have used natural honey for medicinal purposes [23]; however, if it involves cardiovascular diseases, the majority of prior research has been performed on animals and focused on the effectiveness of honey on different cardiovascular risk factors viz. hyperlipidemia, free radicals generation, etc [24]. Vitamin C, flavonoids, polyphenolics, and mono phenolics are some of the antioxidants found in honey. Frequent intake of flavonoids is linked to a reduced risk of cardiovascular illnesses. Honey has an extensive number of phenolic compounds which demonstrate promise in the treatment of cardiovascular conditions. Antithrombotic, anti-ischemic, antioxidant, vasorelaxant, and anti-atherogenic [25] properties are the key defensive outcomes of phenolic compounds in coronary heart disease (CHD). By enhancing coronary vasodilatation, reducing the clotting ability of platelets in the blood, and inhibiting low-density lipoprotein (LDL) oxidation, flavonoids are believed to reduce the risk of CHD by those three main mechanisms [26]. A hypothetical scheme explaining the cardioprotective benefits of honey flavonoids is given in Fig. 2.

Testing of the natural honey was done in 38 overweight people to see how it affected fasting blood glucose, body weight, total cholesterol, triacylglycerol, low-density lipoprotein cholesterol (LDL-C), and C-reactive protein (CRP). The study findings demonstrated that consuming natural honey (70 g) intended for 30 days reduced LDL-C, CRP (P infarction effects in rats), total cholesterol, and triacylglycerole [27].

A study found that pre-treatment of anesthetized rats with natural honey before adrenaline injection protected them from epinephrine-induced vasomotor dysfunction and cardiac disorders while maintaining the positive inotropic effect of adrenaline. This study denotes natural honey's cardioprotective as well as therapeutic effects were directly and indirectly mediated [28].

The effectiveness of honey on blood platelet functioning (assessed using platelet aggregation) and coagulation processes (measured as activated partial prothrombin time (APTT), thrombin time (TT), prothrombin time (PT), and fibrinogen level) were investigated *in vitro*. At 3.75 % and 7.5 % concentrations, honey prolonged APPT, TT, and PT and inhibited aggregation of platelets with an IC50 of 5–7.5 %. Incubation with 6.25 % and 11.75 % honey also decreased the fibrinogen content of platelet-poor plasma.; a 13 % decrease was seen after the addition of 6.25 % honey in comparison to control samples without honey [29].

Honey possesses anti-platelet and antithrombotic properties, thus when utilized in Kyuang-OK-KO (KOK) which is a traditional

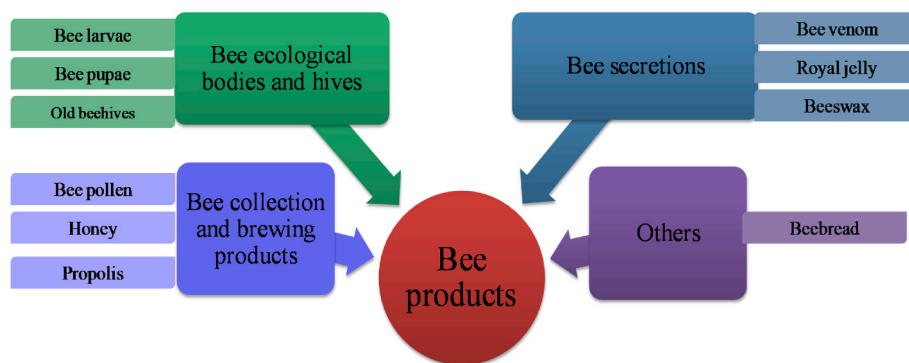


Fig. 1. Bee products and their core compounds.

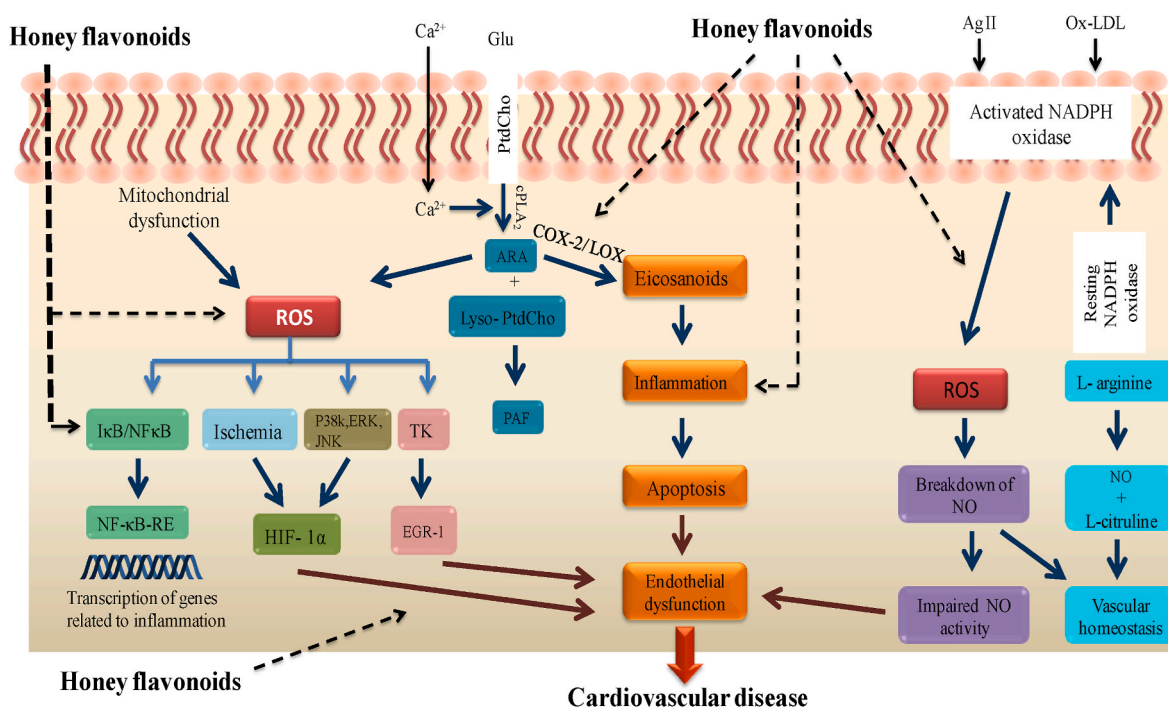


Fig. 2. A hypothetical illustration explaining the cardioprotective benefits of honey flavonoids by their ability to modify cellular signaling pathways.

prescription containing *Rehmannia glutinosa* var. *purpurea* Makino (Scrophulariaceae) (32.0 %), *Lycium chinense* Miller (Solanaceae) (0.9 %), *Aquillaria agallocha* Roxburgh (Thymelaeaceae) (0.1 %), *Poria cocos* Wolf (Polyporaceae) (8.0 %), *Panax ginseng* C.A. Meyer (Araliaceae) (2.8 %), honey (38.5 %), with simple syrup (17.7 %), inhibiting collagen-induced platelet aggregation and shape change. KOK acts by inhibiting ATP release, intracellular Ca^{2+} elevation, and phosphorylation of PLC γ and protein kinase. It reduced thrombosis in mice models and displayed anti-platelet effects during an *in vitro* study. However, demonstrating honey's anti-platelet and antithrombotic actions is challenging due to the use of a food mixture containing honey [30].

Evaluation of the activity level of antioxidant enzymes and the concentration of thiobarbituric acid reactive substances (TBARS), an indicator of lipid peroxidation, were performed to figure out that tualang honey prevented oxidative stress and had a cardioprotective effect. For this experiment, for 45 days, 40 male albino Wistar rats were administered 3 g/kg/day of Tualang honey orally [31].

Nigerian honey (at a dose of 1 and 2 g/kg) reduced hyperlipidemia among a group of diabetic rats fed alloxan. Honey was provided to diabetic rats for three weeks orally. After this time frame, there was an increase in high-density lipoprotein cholesterol (HDL-C) levels and a

decrease in triglyceride and very low-density lipoprotein cholesterol (VLDL cholesterol). Moreover, 1 and 2 g/kg of honey significantly reduced hyperglycemia. Rats with diabetes had initially decreased blood glucose levels (by around 40 %) when administered 1 g/kg body weight of honey [32].

Comparing Tualang Honey and Honey Cocktail, a mixture of honey, royal jelly, and bee bread, over time for their impact on postmenopausal women's anthropometric measures and cardiovascular parameters aged 45–65 were examined. Among postmenopausal women, a double-blinded, randomized, two-armed parallel study was carried out to compare 20 g/day of tualang honey against 20 g/day of Honey Cocktail. The diastolic blood pressure of the tualang honey group was significantly lower than that of the Honey Cocktail group at 12 months, going from 77.92 mmHg at baseline to 73.45 mmHg. When comparing the tualang honey group to the Honey Cocktail group, additionally, the fasting blood sugar level significantly decreased, which went from 6.11 mmol/L at baseline to 5.71 mmol/L at 12 months. When Tualang Honey was added, the results were better [33].

The antiplatelet effects of honey and aspirin using mouse bleeding times were compared. Four groups of mice were given aspirin, honey, placebo, and aspirin. For 12 days, the suspension was administered

orally. For the placebo group, the mean bleeding duration was 102.88 s; for the aspirin group, it was 369.38 s; and for the honey group, it was 304.63 s. The aspirin and honey groups outperformed the placebo group in the Mann-Whitney test, but the aspirin group did not differ significantly from the honey group [34].

The effects of long-term oral naturally occurring honey on cardiac arrhythmias, caused by ischemia/reperfusion were investigated. For 45 days, four groups of male Wistar rats were given natural honey to eat. The hearts were isolated, put on a Langendorff apparatus, and perfused with a modified Krebs-Henseleit solution after being put under anesthesia. To analyze cardiac arrhythmias, ECGs were recorded. The number and duration of ventricular tachycardia (VT), ventricular ectopic beats (VEBs), and reversible ventricular fibrillation (Rev VF) were all significantly decreased by honey, according to the results. In the natural honey group, the occurrence of VT decreased to 22 % during the reperfusion period. The outcomes of the study imply that increased hemodynamic functions, energy sources like glucose and fructose, and antioxidant activity may be in charge of these outcomes [27]. The effects of long-term oral natural honey on cardiac arrhythmias caused by ischemia/reperfusion were investigated. For 45 days, four groups of male Wistar rats were given natural honey to eat. The hearts were isolated, put on a Langendorff apparatus, and perfused with a modified Krebs-Henseleit solution after being put under anesthesia. To analyze cardiac arrhythmias, ECGs were recorded. The number and duration of ventricular tachycardia (VT), ventricular ectopic beats (VEBs), and reversible ventricular fibrillation (Rev VF) were all significantly decreased by honey, according to the results. In the natural honey group, the incidence of VT decreased to 22 % during the reperfusion period. The results of the study imply that increased hemodynamic functions, energy sources like glucose and fructose, and antioxidant activity may be in charge of these outcomes [27].

Honey flavonoids limit free radical damage to endothelial cells by reducing the generation of ROS and eicosanoids. By preventing LDL cholesterol from being oxidized, flavonoids stop atherosclerotic plaque from forming. Moreover, the expression of HIF-1 is modulated by honey flavonoids, suggesting their involvement in maintaining heart function. Genes that cause oxidative stress and inflammation are not expressed when honey flavonoids prevent NF- κ B from activating and translocating to the nucleus. Reactive oxygen species (ROS), reactive nitrogen species (RNS), Phosphatidylcholine (PtdCho), cytosolic phospholipase A2 (cPLA2), arachidonic acid (ARA), lyso-phosphatidylcholine (lyso-PtdCho), platelet activating factor (PAF), Thioketal (TK), early growth response protein 1 (EGR1), hypoxia-induced factor-1 α (HIF-1 α), Inhibitor of κ B (I κ B), nuclear transcription factor-kappaB (NF- κ B), cyclooxygenase-2 (COX-2), Oxidized low density lipoprotein (Ox-LDL), nitric oxide (NO).

3.2. Propolis

Propolis, a plant-secreted substance, is used in beehive protection by applying thin layers to the inner walls of the hive. It sterilizes the environment, reduces entry, covers cracks, and strengthens comb edges, acting as a protective agent and social immunity [35,36]. Propolis and its constituents are successful in the treatment and prevention of cardiovascular risk factors including atherosclerosis, hypertension, dyslipidemia, obesity, and diabetes [37].

The effects of different propolis extracts on platelet aggregation against 3 platelet agonists: 10 μ M ADP, 50 μ M thrombin receptor activator peptide, and 5 μ g/mL collagen were investigated. They inhibited those agonist-induced platelet aggregations in a dose-dependent manner [37].

The anti-aggregatory potential of propolis ethanolic extracts on whole blood was demonstrated at low micromolar concentrations. This effect may be partially attributed to the polyphenolic constituents of propolis. According to the study's findings, propolis supplements may be able to improve platelet aggregation function tests and may even be able

to prevent cardiovascular illnesses [38].

The anti-platelet properties of propolis are thought to be attributed to flavonoids, which are the main constituents [37,38]. By inhibiting different enzymes within intracellular signaling pathways, such as phospholipase C and A2, and cyclooxygenase, they are known to prevent blood platelet aggregation induced by thrombin, ADP, and collagen. Furthermore, flavonoids may lessen nitric oxide production and the oxidative burst. Remarkably, several writers suggest that propolis may be cardioprotective *in vivo*.

Total flavonoids of propolis (TFP) significantly inhibited the increase in (Atrial natriuretic factor) ANF and β -MHC mRNA levels in mice that had pathological cardiac hypertrophy (PCH) induced by isoproterenol (ISO) in a dose-dependent manner. Treatment with TFP considerably reduced adverse cardiac dysfunction, hypertrophy, and related disorders like fibrosis. TFP therapy greatly minimized cardiac remodeling and apoptotic damage, which were connected with the PI3K/AKT signaling pathway.

Propolis reduced body weight, reduced blood lipid levels, and inhibited neointimal hyperplasia in rabbits with hypercholesterolemia. Propolis also attenuated lipid deposition, and collagen fiber, and reduced oxidative stress. It also hampered the expression of Toll-like receptor 4 and NF- κ B, suggesting it could improve vascular inflammation. The findings could inform future studies on vascular restenosis prevention and treatment [39].

The TFP inhibits the rat cardiac cell apoptosis with chronic heart failure that is triggered by adriamycin. Additionally, Cx43 expression, particularly the phosphorylation state, may be governed by utilizing a propolis preparation. Caffeic acid phenethyl ester (CAPE) is one of propolis' most potent constituents. Initially discovered to be a part of propolis, CAPE can be removed from propolis miscellaneous techniques [40].

Trigonula sapiens stingless bees were gathered in South Sulawesi, Indonesia, and used to create three different types of extracts: ethanolic extract of propolis (EEP), spray-dry propolis without wax (SDPNW), and spray-dry propolis with wax (SDPW). The propolis extracts undertook ACE inhibitory activity testing, total phenolic and flavonoid content measurement, and physicochemical screening, among other procedures. The propolis extracts were subjected to phytochemical screening to assess any possible secondary metabolites. Alkaloids, flavonoids, saponins, tannins, quinones, steroids, triterpenoids, essential oils, and coumarins are generally present in all propolis preparations in a qualitative manner. Out of the two extracts, the EEP exhibited the highest color intensity in this instance. The IC₅₀ values for the ACE inhibitory action on captopril, EEP, SDPNW, and SDPW were 5.97, 115.06, 112.93, and 116.70 ppm. SDPNW had a greater TFC and TPC content (1.59 % and 1.93 %, respectively) than EEP and SDPW. It may be concluded that Indonesian propolis extract satisfies extraction criteria and may help lower the risk of hypertension and diabetes [41].

3.3. Bee pollen

Bee pollen is the chief source of proteins for bees. This product is what emerges when worker bees use salivary substances and nectar to agglutinate flower pollen, depositing the mixture into the hive. Alongside protein, pollen is a good supply of fats, vitamins, minerals, as well as certain carbohydrates [42].

H2O2-induced apoptosis in H9c2 cardiomyocytes and the impact of *Schisandra chinensis* bee pollen extract. Nine derivatives containing quinic acid, three nucleotides, and two carbohydrates were identified. It was also discovered that the tested extract (12.5, 25, and 50 μ g/mL) had beneficial antioxidant qualities, such as raising the concentration of glutathione and myocardial superoxide dismutase activity as well as lowering the level of malondialdehyde in the heart *in vitro* [43].

In rat models of acute myocardial infarction triggered using isoprenaline cardioprotective and antioxidant properties of *S. chinensis* bee pollen extract were investigated [44]. The tested extract's

cardioprotective effects may be interrelated to its antioxidative qualities, according to the authors. Additionally, they speculate that the rat heart's upregulation of antioxidant enzyme activity, which is regulated by the transcription factor Nrf2, may be an adaptive response to oxidative stress and myocardial infarction caused by isoprenaline. Rats given the extract also showed increased heart protein expression of heme oxygenase-1 and B-cell lymphoma protein 2 (Bcl 2), but decreased heart protein expression of (Bcl-2-associated X) Bax protein. These findings might suggest that bee pollen extract, by controlling Bcl-2 and Bax, could lessen cardiocyte apoptosis. Bee pollen's antioxidant potential has also been documented by other authors [39,45].

The bee pollen extract, rich in polyphenols, may have anti-atherogenic properties, and the extract on high-fat diet-induced Apo-knockout mice. The extract reduces cholesterol, oxidative stress, and coronary artery damage, limiting or preventing atherosclerosis. It also inhibited atherosclerosis by reducing angiotensin-converting enzyme activity and angiotensin II levels [46].

To treat patients with atherogenic dyslipidemia, the effectiveness of bee products, such as honey, pollen, and bee bread was tested on 157 patients (93 women and 64 men). The most significant finding is that no participant getting bee food products showed signs of a specific allergy or intolerance to honey, bee bread, or pollen. Both test groups showed significant hypolipidemic activity; patients receiving honey and pollen saw an 18.3 % decline in total cholesterol, while those receiving bee bread saw a 15.7 % decrease in total cholesterol. Further research revealed that the application of honey and pollen only boosted blood lipid composition regarding body mass loss in patients classified as overweight (BMI: 25–30) or obese (BMI >30) [47].

Male rats given hypertensive treatment with L-NG-nitro arginine methyl ester (L-NAME) were used in a study to examine the preventive and therapeutic effects of ethanolic extracts of propolis and pollen on breeding function. Groups I through IV comprised the control group of rats, L-NAME group II, L-NAME and propolis group III, and L-NAME and pollen group IV. According to research, the examined bee products seemed to affect reproductive function by reducing the performance of the acting inflammatory pathways [48].

Forty volatile chemical components were identified from the bee pollen extract by advanced phytochemical screening of volatile chemical contents examined by GC-MS. Of these, the bee pollen compounds, associated with the hypocholesterolemic effect were examined using the *in silico* docking approach. Oxidosqualene: lanosterolcyclase (OSC) was selected as the target enzyme, aiding in the production of cholesterol. Using Ro 48–8071 fumarate as a typical enzyme inhibitor and a selection of ligands including hexadecanoic acid, pentadecanoic acid, pyrrolidone, and α -amyrin, all of the ligands efficiently coupled with the target enzyme OSC, according to molecular docking study. α -Amyrin demonstrated the greatest binding interaction energy (–13.37 kJ mole⁻¹) of the four chemicals with the target enzyme. The weight-reducing ability and hypocholesterolemic impact of bee pollen may be caused by the inhibition of the OSC enzyme [49].

3.4. Royal jelly (RJ)

Through their mandibular and hypopharyngeal glands, worker bees manufacture royal jelly (RJ). RJ has an acidic taste, is viscous, and ranges in color from white to yellow. Proteins, fatty acids, sugars, and minerals are among its complex constituents [50]. RJ is used throughout the queen's life and for a brief time during the feeding of the larvae [42].

Major royal jelly protein 1 (MRJP1) is a potential therapeutic target for hypertension. Its mode of action could involve controlling the contraction, migration, and proliferation of vascular smooth muscle cells, an essential part of the arterial wall and a major regulator of blood pressure. Moreover, RJ seems to have hypocholesterolemic qualities [51].

The hypocholesterolemic protein MRJP1 was found in RJ [52] and has been shown to have higher hypocholesterolemic activity than

β -sitosterol. In the opinion of the authors, the substance under investigation may control the blood lipid profile, lowering dehydroepiandrosterone sulfate levels [53].

The impacts of RJ (150 mg/day) on bone turnover and cardiovascular indicators in 36 clinically healthy postmenopausal women have been studied [54]. The subjects were given RJ for a duration of three months. It was discovered that 63 % of dry weight fat content of the RJ used in the study was made up of medium-chain fatty acids, or substances with hypolipidemic qualities. Significant increases in HDL-C and significant reductions in LDL and TC were the outcomes of the treatment. Supplementing with RJ, according to the authors, may provide a different approach to treating dyslipidemia linked to menopause.

As per a recent meta-analysis [55], consuming RJ could potentially enhance lipid parameters. A search was carried out through PUBMED, the Cochrane Library, Scopus, Web of Science, and Google Scholar to find studies examining the impact of RJ on adult blood lipid parameters up until July 2017. Triglyceride, LDL, and HDL-C blood concentrations did not significantly change, according to the pooled analysis of six trials that followed, but total cholesterol blood levels were found to be reduced by RJ.

RJ can prevent heart tissue damage caused by fluoride by activating the nrf-2/NF- κ B and bcl-2/bax signaling pathways, as evidenced by recent findings [56]. There were forty-two rats in this experiment. RJ was administered five times a week for eight weeks at a single dose of 100 mg/kg.

In 55 postmenopausal women experiencing menopausal complaints, Georgiev and colleagues investigated the effects of a dietary supplement called Melbrosia that combined flower pollen, Perga (fermented flower pollen), and RJ over the course of three months. After taking two capsules of Melbrosia once a day for the first two weeks, the patients were given one capsule every ten days. TC, LDL-C, and HDL-C were found to significantly decrease and significantly increase with the treatment, respectively. These changes might have some impact on the risk of CVD [57].

Celecoxib, a COX-2 selective inhibitor of the NSAIDs category, is used to treat both acute and chronic pain as well as other inflammatory conditions. Sadly, there is a strong correlation between its long-term use and dangerously aberrant cardiovascular events. A study was designed to explore the effect of long-term administration of celecoxib on the cardiac tissues of male albino rats. The study also focused on the putative cardioprotective benefit of RJ. Thirty, male albino rats were randomly allocated into 3 equal groups; 10 each [1]: rats served as the control group and got no treatment [2]; rats received celecoxib (50 mg/kg/day, orally), for 30 consecutive days [3]; rats received celecoxib (50 mg/kg/day, orally) with RJ (300 mg/kg/day, orally) for 30 consecutive days. To measure the levels of antioxidants and oxidants in the heart, sera were collected. Male albino rats administered celecoxib for an extended period developed cardiotoxicity, as evidenced by significantly elevated serum levels of creatine phosphokinase (CPK), creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH). RJ was found to have ameliorative effects against celecoxib-induced cardiotoxicity, as evidenced by significantly decreased levels of CPK, CK-MB, and LDH. Malondialdehyde (MDA) levels, an indication of oxidative stress, and the bax gene were significantly decreased. It also showed notable increases in superoxide dismutase (SOD) and the bcl-2 gene, which may be involved in its protective benefits against celecoxib-induced cardiotoxicity [58].

3.5. Bee venom

Through their stinger, which serves as an inoculation tool, bees produce bee venom (BV). Only females can sting because the stinger evolved from the laying apparatus. The poisonous gland present in the abdominal cavity produces a complex substance called apitoxin or bee venom [59].

Bee venom can modulate heart rate variability and improve cardiac

function. Melittin, a major polypeptide in bee venom, has been found to ameliorate coxsackievirus B3-induced myocarditis, a disease-causing sudden death in children and young people. Treatment with melittin reduced myocardial cell apoptosis, decreased expression of Bax and caspase-3, and increased bcl-2 [40].

The effects of apitoxin or bee venom, a naturally occurring product with anti-inflammatory, hypoglycemic, hypolipidemic, and antioxidant properties, on cardiac dysfunction in diabetic hyperlipidemic rats were investigated. For the investigation, 50 mature male albino rats were employed and were split into five groups, one of which served as a negative control and the others as injection sites for streptozotocin and nicotinamide, which were used to cause type 2 diabetes. Following the confirmation of diabetes, the rats were given a four-week high-fat diet. For four weeks, the rats received treatment with atorvastatin, metformin, and bee venom. Heart tissue and blood samples were collected. The findings revealed a significant drop in the levels of malondialdehyde, nuclear factor-kappa- β (NF- κ B), vascular cell adhesion, glucose, total cholesterol (TC), triacylglycerol, LDL-C, troponin I, creatine kinase (CK), and lactate dehydrogenase (LDH) activities [60].

An inflammatory response to lipids and calcareous deposits in the vascular wall results in atherosclerosis. Recent studies have shown the significance of regulatory T (Treg) cells as a novel atherosclerosis treatment. By inducing Treg cells, this study suggested that bee venom phospholipase A2 (bvPLA2) may be a potential therapeutic agent for atherosclerosis. The effects of bvPLA2 on atherosclerosis were studied in mice. This study's findings demonstrate that bvPLA2 enhanced Treg cells, which were then followed by a decline in the development of foam cells and lipid buildup in the aorta and aortic valve. Notably, it was discovered that Treg cells are necessary for the effects of bvPLA2. The results of this study point to bvPLA2 as a possible treatment for atherosclerosis [61].

3.6. Beeswax

Utilizing the ceriferous glands in the ventral region of the abdomen, bees create beeswax to build their combs. The honeycomb is used for laying eggs, developing young bees, and storing honey, pollen, and RJ in addition to other purposes [62]. The colony's growth phase is when wax production peaks. It mostly consists of higher fatty acid and alcohol esters. Beeswax also includes trace amounts of alcohols, free acids, hydrocarbons, and other compounds in addition to esters [3].

In this work, the effects of beeswax alcohol (BWA) on zebrafish embryo survival, LDL oxidation prevention, and increased paraoxonase 1 (PON-1) activity in high-density lipid & protein (HDL) are assessed. The results demonstrate that BWA significantly outperforms coenzyme Q10 in augmenting PON-1 activity. Additionally, BWA lessens lipid peroxidation in LDL and returns LDL to its original size and shape [63].

3.7. Bee bread

Bees generate a pollen-based product that microorganisms use to ferment lactic acid, converting it into "bee bread" after it has been collected and stored inside the hive [64,65]. bee bread hydrolysates have antioxidant qualities that are comparable to 1 mM α -tocopherol when measured by scavenging hydroxyl and superoxide anion radicals [66]. Additionally, it was discovered that the bread inhibited the angiotensin I-converting enzyme (ACE) similarly to other fermented foods like fish sauce, miso, sake, and natto.

4. The molecular mechanism underlying cardioprotective effects of bee products

In both human and animal models of cardiovascular disease, high oxidative stress increases the production of free radicals, lowers antioxidant levels, and depletes enzymes that scavenge free radicals. the production of ROS (Reactive Oxygen Species) can result in endothelial

dysfunction, vascular smooth muscle cell growth, arteriogenesis, and vascular smooth muscle death [67–69]. Atherosclerosis is a condition where arterial thickening is dependent on the microvasculature and may be accompanied by inflammation and oxidation-driven angiogenesis [70]. Intracellular ROS generation is stimulated by proatherogenic agents such as oxidized low-density lipoprotein (LDL), proinflammatory cytokines, and angiotensin II, which in turn promotes [71–73]. ROS are produced in the arterial wall by NADPH oxidase isoforms in the proximity of hypertension, hypercholesterolemia, diabetes, aging, and atherosclerosis [74]. Additionally, consuming more polyphenols may lower the incidence of cardiovascular diseases. Cardiovascular disease may also be exacerbated by monoamine oxidase A (MOA) activity [75]. Disorders like hypertension, atherosclerosis, restenosis, and heart failure may be brought on by ROS-induced endothelial cell damage or vascular smooth muscle growth [76].

Honey, being high in flavonoids, may be used therapeutically by lowering blood pressure, treating conditions like dyslipidemia and hyperinsulinemia, and enhancing cardiovascular risk factors like endothelial function and inhibition of LDL oxidation. It has been documented that naringenin treatment corrects obesity, hyperinsulinemia, and dyslipidemia, which attenuates atherosclerosis in a mouse model of cardiovascular disease [77]. Honey has flavonoids that fall into the chemical classes of flavones, which include acacetin, apigenin, chrysin, luteolin, 5-hydroxyflavone, 5-methoxy flavone, 7-hydroxyflavone, and flavanones, which include hesperetin, pinocembrin, 4'-hydroxyflavanone, and 6-hydroxyflavanone [78]. Additionally, honey has vasorelaxing properties. One antioxidant flavonol linked to a reduced risk of stroke and coronary heart disease is quercetin. Flavonoids that chelate intracellular iron and suppress the production of OH $^{\bullet}$, such as quercetin, chrysin, luteolin, and 3,6-dihydroxyflavone, may be useful as protective agents in pathological cardiac conditions caused by oxidative stress related to metal overload [79,80]. hesperetin possesses antiplatelet and anti-aggregatory properties [81], whereas kaempferol significantly relaxes isolated porcine coronary artery rings. It has been demonstrated that propolis, an active ingredient in propolis, reduces oxidative stress because of its antioxidant qualities [82].

5. Challenges and adaptations of bee products in a modern context

A significant challenge still lies in comprehending and navigating this complex web of stressors to lower colony losses and enhance honey bee health [83]. Land-use intensification—which results in habitat loss from agriculture and urban development—as well as the spread of invasive species, diseases, and pesticides, are all contributing factors [84–86]. The use of agricultural chemicals such as fungicides and insecticides is having an increasingly noticeable detrimental effect on bee health, as evidenced by the death of commensal microbes [87,88]. Global climate change is impacting bee populations, with an expected rise in the disappearance of essential pollinators [89]. The documented impact of these changes on the global decline of bumble bees has already occurred on multiple continents [90]. These elements have an impact on bee product standardization and quality control. Beekeepers are adapting by promoting bee-friendly environments and sustainable practices to prevent adulteration and maintain consistent product quality. Innovative beekeeping methods are fueled by research and creativity, which increases honey yield. Product authenticity is confirmed through certification programs, which increase customer confidence. Sustainable beekeeping requires balancing scientific discoveries, conservation efforts, and public awareness.

6. Future exploration and research needs

For centuries, bee products have been utilized for their purported health benefits, including propolis, honey, and RJ [91]. Table 1 summarizes the cardioprotective potential of some bee products in different

Table 1Some investigated the cardioprotective role of bee products in *in vitro* and *in vivo* models.

Bee product	Investigated role	Procedure	<i>In vitro/in vivo</i> and Models used	Findings	References
Honey	Cardioprotective agent	Pretreatment with natural wild honey (5 g/kg) for 1 h before the injection with epinephrine (100 µg/kg)	<i>in vivo</i> (Sprague-Dawley albino Rats)	Several ameliorative outcomes to the ECG parameters and vasomotor dysfunction of anesthetized stressed rats thus protected from the incidence of epinephrine-induced cardiac disorders and vasomotor dysfunction.	(26)
Tualang Honey versus Honey Cocktail (mixture of honey, bee bread, and royal jelly)	Anti-hypertensive effect	A randomized, double-blinded, two-armed parallel study comparing 20 g/day of Tualang Honey vs 20 g/day Honey Cocktail among postmenopausal women aged 45–65 years and were assessed at baseline, 6 months, and 12 months of the intervention.	<i>In vivo</i> (postmenopausal women)	Significant decrease in the diastolic blood pressure from 77.92 mmHg at baseline to 73.45 mmHg at 12 months and a significant decrease in the fasting blood sugar from 6.11 mmol/L at baseline to 5.71 mmol/L at 12 months in the Tualang Honey group compared to the Honey Cocktail group.	(33)
Honey	Antiplatelet effect	Honey suspension(75 mg) has given orally for 12 days and compared with aspirin(80 mg)	<i>in vivo</i> (Double Ditsch Webster mice)	No significant differences in the aspirin group against honey	(34)
Water Extract of Propolis	Anti-aggregatory potential	Platelet-rich plasma was prepared and incubated <i>in vitro</i> with different concentrations of the tested extracts and components of flavonoids	<i>In vitro</i> Whole blood (Healthy human volunteers)	Water Extract of Propolis exhibited dose-dependent inhibitory effects on platelet aggregation	(37)
Melittin a major polypeptide in honey bee venom	Anti-inflammatory action	Mice had been infected with Coxsackievirus B3(CVB3) for 24 h, melittin was injected intraperitoneally for 7 consecutive days (0.1 mg/kg)	<i>In vivo</i> (BALB/c mice)	Replication of CVB3 was inhibited by melittin, alleviated myocardial injury in CVB3-induced mice, suppressed the activity of f AST, CK, HBDH, and LDH	(40)
Honey	Anti-arrhythmic activity	Rats were fed with natural honey(1 %, 2 %, and 4 % dissolved in the drinking water) for 45 days except for the control group.	<i>in vivo</i> (Male Wistar Rats)	Reduced number and duration of ventricular tachycardia significantly reduced the of ventricular ectopic beats(VEBs). Additionally, the incidence and duration of reversible ventricular fibrillation (Rev VF) were lowered by honey (2 %)	(92)
Sundarban Honey	Protection against ISO-induced oxidative stress in the myocardium.	Rats were pretreated with Sundarban honey (5 g/kg) daily for a period of 6 weeks. After the treatment period, ISO (85 mg/kg) was subcutaneously injected into the rats at 24-h intervals for 2 days.	<i>in vivo</i> (Adult male Wistar Albino rats)	Reduced levels of serum troponin I, a significant decrease in the activities of CK-MB, LDH, AST, and ALT	(93)
Honey	Cardioprotective agent	Pretreatment with natural wild honey (5 g/kg) for 1 h before the injection with epinephrine (100 mg/kg)	<i>in vivo</i> (Sprague-Dawley albino Rats)	Several ameliorative outcomes to the ECG parameters and vasomotor dysfunction of anesthetized stressed rats thus protected from the incidence of epinephrine-induced cardiac disorders and vasomotor dysfunction.	(26)
Tualang honey	Cardioprotection of Tualang honey against cardiovascular diseases	Male albino Wistar rats (n = 40) were pretreated orally with Tualang honey (3 g/kg/day) for 45 days. Subcutaneous injection of ISO (85 mg/kg in saline) induced myocardial infarction	<i>in vivo</i> (Male albino Wistar rats)	Reduced serum cardiac marker enzyme activities (CK-MB, AST, and LDH)	(31)
Water extract of propolis	Anti-aggregatory potential	The effect of five selected flavonoids (pinocembrin-7-methyl ether, epicatechin, hesperetin, 6-hydroxy flavone, and 3,6-dihydroxyflavone) on platelet aggregation was studied in the citrated whole blood samples and five different aggregation inducers (ADP, arachidonic acid, collagen, ristocetin and TRAP-6) were used	<i>In vitro</i> Whole blood (Healthy human volunteers)	Minimal antiaggregatory concentrations of flavonoids were reported in the following ranges: 0.12–1.91 µM; 15.26–244.14 µM; 15.26–122.07 µM; and 0.06–15.26 µM for ADP, collagen, TRAP-6 and ristocetin aggregation-inducers, respectively. When arachidonic acid was used for induction of platelet aggregation, a proaggregatory effect was observed for pinocembrin-7-methyl ether, epicatechin, hesperetin, and 3,6-dihydroxyflavone, while the expected antiaggregatory effect was observed only for 6-hydroxy flavone	(45)
Ethanol extract of propolis	Anti-aggregatory potential	Platelet aggregation was tested by impedance aggregometry on the whole blood samples of ten healthy volunteers.	<i>In vitro</i> Whole blood samples (Healthy human volunteers)	Samples of propolis with lower content of luteolin and higher content of pinocembrin-7-methyl ester showed better antiplatelet	(38)

(continued on next page)

Table 1 (continued)

Bee product	Investigated role	Procedure	<i>In vitro/in vivo</i> and Models used	Findings	References
Propolis	Inhibitory action on apoptosis of myocardial cells of chronic heart failure	Six male SD rats were used as a chronic heart failure (CHF) model, divided into five groups: CHF, total flavonoids of propolis low dose, middle dose, high dose, and digoxin group. After six weeks, cardiac function indexes, brain natriuretic peptide, cardiac troponin I, TNF- α , IL-6 content, myocardial morphological changes, collagen fiber hyperplasia, myocardial apoptosis, and protein connexin 43 (P-Cx43) expression were detected.	<i>In vivo</i> (Sprague Dawley Rats)	activity i.e. lower values of minimal antiaggregatory concentration. The CHF group showed improved plasma BNP, cTnI, TNF- α , and IL-6 content. P-Cx43 expression was higher in the CHF group than in the NC group, and the myocardial apoptosis index was higher in the CHF group.	(94)
Bee pollen of <i>S. chinensis</i> (Turcz.) extract	Antioxidant and cardioprotective effect	The rats were intragastrically administrated with bee pollen extract (600, 1200, or 1800 mg/kg/day) and Compound Danshen dropping pills (270 mg/kg/day) for 30 days, then subcutaneously injected with ISO (65 mg/kg/day)	<i>In vivo</i> (Sprague Dawley rats)	Pretreatment with middle and high doses of bee pollen extract significantly reduced serum CK-MB, AST, and LDH activities and increased myocardial superoxide dismutase, glutathione peroxidase, and catalase activities.	(44)
Polyphenol-rich extract from bee pollen	Antioxidant and anti-atherogenic effect	The extract was given with feed in two doses of 0.1 and 1 g/kg body mass. The following factors were estimated: TC, oxidized LDL, asymmetric dimethylarginine (ADMA), ANG II, and ACE	<i>In vivo</i> (C57BL ₆ ApoE-knockout mice)	Extract reduced oxidative stress by lowering the levels of ox-LDL, ADMA, ANG II, and ACE.	(46)
Royal jelly (RJ)	Anti-hypercholesterolemic effect	Subjects with mild hypercholesterolemia (180–200 mg/dL) were randomly selected and divided into two groups as experimental or placebo, who requested to intake nine capsules (350 mg/capsule) of RJ or placebo/day, respectively, for three months	<i>In vivo</i> (Mildly hypercholesterolemic adults)	The serum TC and LDL-C levels declined significantly after RJ administration. However, triglyceride and HDL-C levels were barely altered	(53)
Royal jelly	Anti-hypercholesterolemic effect	Participants received 150 mg of RJ daily for three months. Circulating cardiovascular risk markers and bone turnover parameters were compared between the baseline and the three-month visit.	<i>In vivo</i> (Postmenopausal healthy women)	A significant increase in HDL-C, LDL-C and TC	(54)
Royal jelly	Antioxidant action	RJ was fed at (100 mg/kg) and compared against a control group	<i>In vivo</i> (Male Wistar albino rats)	MDA levels and Bcl-2, Gsk-3, and NF- κ B protein expression levels were decreased in the RJ-applied groups	(56)

in vitro and *in vivo* models. Nonetheless, the assertion that bee products in particular have a direct effect on cardiovascular diseases is not well-supported by empirical scientific research. The scientific community has not yet come to a consensus on the relationship between the consumption of bee products and cardiovascular diseases, despite the long history of traditional use and anecdotal evidence suggesting health benefits. Regarding the impact of consuming bee products on cholesterol levels and cardiovascular health, research has produced contradicting findings. There is still disagreement in the scientific community regarding the link between the consumption of bee products and cardiovascular diseases, despite a long history of traditional use and anecdotal evidence indicating health benefits. For conclusive answers, more investigation and analysis are needed in the ongoing debate about the intake of bee products by heart patients.

7. Future exploration and research needs

For centuries, bee products have been utilized for their purported health benefits, including propolis, honey, and RJ [91]. Table 1 summarizes the cardioprotective potential of some bee products in different *in vitro* and *in vivo* models. Nonetheless, the assertion that bee products in particular have a direct effect on cardiovascular diseases is not well-supported by empirical scientific research. The scientific community has not yet come to a consensus on the relationship between the

consumption of bee products and cardiovascular diseases, despite the long history of traditional use and anecdotal evidence suggesting health benefits. Regarding the impact of consuming bee products on cholesterol levels and cardiovascular health, research has produced contradicting findings. There is still disagreement in the scientific community regarding the link between the consumption of bee products and cardiovascular diseases, despite a long history of traditional use and anecdotal evidence indicating health benefits. For conclusive answers, more investigation and analysis are needed in the ongoing debate about the consumption of bee products by heart patients.

8. Conclusion

The cardioprotective potential of honey, propolis, RJ, bee pollen, beeswax, bee venom, and bee bread has been outlined in this review. Honey and other bee products also seem to have some potential for heart health benefits. Unfortunately, only a small number of *in vivo* research have been carried out in human models, even though this potential has shown promise *in vitro* as well as in animal and human models. Additionally, no hard clinical data supporting the safety or effectiveness of apitherapy treatments has been found to date, and there are no guidelines for the safe or effective dosages of bee products to be used in the prevention and treatment of CVDs. Despite all of its drawbacks, apitherapy offers new insights into its well-performed role in the

management and prevention of cardiovascular diseases, in this natural products-focused era instead of going towards chemically derived ones so that more specific desirable outcomes can be achieved while excluding unfavorable side effects.

CRedit authorship contribution statement

Rimpa Karmakar: Data curation, Conceptualization. **Sakshi Soni:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Vandana Soni:** Writing – review & editing, Visualization. **Umesh Kumar Patil:** Writing – review & editing, Writing

– original draft, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CVD	cardiovascular disease
CHD	coronary heart disease
LDL-C	low-density lipoprotein cholesterol
HDL-C	high-density lipoprotein cholesterol
CRP	C-reactive protein
APTT	activated partial prothrombin time
TT	thrombin time
PT	prothrombin time
KOK	Kyung-OK-KO
TBARS	thiobarbituric acid reactive substances
ISO	isoproterenol
TFP	total flavonoids of propolis
PCH	pathological cardiac hypertrophy
ANF	Atrial natriuretic factor
CAPE	Caffeic acid phenethyl ester
Bcl 2	B-cell lymphoma protein 2
Bax	Bcl-2-associated X
L-NAME	L-NG-nitro arginine methyl ester
MRJP1	Major royal jelly protein 1
bvPLA2	bee venom phospholipase A2
BWA	beeswax alcohol
PON-1	paraoxonase 1
ACE	angiotensin I-converting enzyme

Data availability

Data will be made available on request.

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