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Effectiveness of Honey Bees Propolis Extract in The Treatment of Type 1 Diabetes Mellitus

(*Efektifitas Ekstrak propolis Lebah Madu pada Pengobatan Diabetes Tipe 1)*

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ABSTRACT

Background: Diabetes Mellitus (DM) is a health problem that affects more than 400 million people worldwide. Type 1 diabetes is an autoimmune disease characterized by damage of pancreatic cells followed by hyperglycemia and oxidative stress. Propolis is one of the natural ingredients of bee products. Propolis is known to have bioactive compounds that are rich in flavonoids, phenolic and antioxidant properties so that it has potential as an antidiabetic. **Objectives:** This writing aims to determine the activity of propolis in test animals of Type 1 DM model. **Methods:** This research method uses a literature study using type 1 diabetic as inclusion criteria in journal screening. Keywords used include propolis, diabetes and hyperglycemia. Literature is obtained through an electronic data base, such as Google Scholar, PubMed, Scopus and Science Direct. **Results:** Based on the articles that have been collected, that Type 1 DM causes inflammation which is characterized by decreased immune function due to increased levels of IL-6, IL-1β and TNF-α. Propolis can reduce levels of pro-inflammatory cytokines, prevent the inflammatory process in diabetes and have hypoglycemic activity. **Conclusions:** The conclusion of the reviewed article that propolis from honey bee has effectiveness to improve the function of body cells and reduce diabetes complication.

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INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by high levels of glucose in blood due to abnormalities in insulin secretion or insulin activity (Marzel 2020). According to the International Diabetes Federation (IDF) it is estimated that in 2021 there will be 537 million people who will be affected by diabetes. Diabetes can be classified into several categories such as Type 1 diabetes, Type 2 diabetes, gestational diabetes mellitus and monogenic diabetes syndromes. Diabetes Mellitus Type 1 was conducted due to autoimmune β-cell destruction and Diabetes Mellitus Type 2 was conducted due to a non-autoimmune progressive loss of adequate β-cell insulin secretion. In the same year, type 1 diabetes mellitus affects almost 1.2 million children and adolescents (Webber 2013).

Diabetes Mellitus Type 1 (DMT1) is characterized by increase in blood glucose levels (hyperglycemia) caused by an autoimmune reaction that causes damage to pancreatic cells resulting in a deficiency of insulin secretion (Katsarou et al. 2017). But there are also those caused by viruses such as the Cocsakie virus, Rubella, Herpes and so on (Hartanti et al. 2013). Pancreatic beta cells can produce insulin where insulin functions to regulate glucose levels in the blood. If the cell damage is found to reach 80-90%, then the symptoms of DM include polyuria, polydipsia, and weight loss begin to appear. This cell damage occurs more rapidly in children than in adults. Most people with DMT1 75% of cases occur before the age of 30 years (Marzel 2020).

Propolis is a honey bee product. Propolis is a sticky resinous constituent that bees collect of plant buds. The propolis produced by bees is used to seal cracks, maintain temperature and humidity so that the bee's sarah is stable and protect them from microbes. Propolis contain of resin, balsam, wax, aromatic oils, pollen , and other composition (Azid, Sabrina, and Jajuli 2020).

The application of propolis in modern medicine has attracted attention because of its chemical composition. Chemical contained in propolis include flavonoids, terpenoids, phenolics and others (Huang et al. 2014). The high bioflavonoids in propolis have antioxidant, antibacterial, antiviral, antifungal, and anti-inflammatory properties. Other substances of propolis also act as a local anesthetic, reduce spasms, heal gastric ulcers and strengthen capillaries (Azid et al. 2020). Propolis has been proven safe and non-toxic to humans both internally and externally (Alvarez-Suarez 2017). There are still limited articles that comprehensively discuss the diabetic effects (DMT1) of honey bee propolis. This literature review aims to analyze how the effectiveness of propolis from honey-producing bees in test animals of the DMT1 model.

MATERIAL AND METHODS

This study uses a narrative review method. The source of this research data is obtained by the search engine on Google Scholar, PubMed, ScienceDirect, Scopus by selecting articles using keywords. The

articles analyzed are articles that use experimental research methods and national and international journals published in 2012-2022. The keyword for screnning was used propolis, diabetes mellitus, hiperglycemia. Inclusion criteria focused on type 1 diabetes and their mechanism.

RESULTS AND DISCUSSION

The effect of propolis supplementation originated from Saudi Arabia was conducted by Al Ghamdi et al. (2015) showed that treatment could interfering mechanism on plasma cytokine profiles, lipid profiles and chemotaxis in a type 1 diabetic rat model. The sample of this study using 39 STZ-induced male mice showed that administration of propolis ethanol extract in test animals can affect the decline levels of IL-6, IL-1β and TNF-α, increase body weight, lower blood glucose level, reduce levels of oxidative reactions (ROS), increase insulin levels and lower cholesterol levels. The research conducted by baligui et al., 2021 (Balingui et al. 2021) is a research experimental study with a sample of 25 male rats induced by Streptozotocin (STZ). In this study, it was shown that nyambaka propolis extract could reduce blood glucose levels using 250 mg/kg and 500 mg/kg propolis, then the percentage reduction in blood sugar levels was 65% and 78.13% and could increase body weight. Research Oladayo, 2016 (Oladayo 2016) showed that Nigerian propolis extract administered with low and high doses (200 mg/kg and 300 mg/kg) for 42 days revealed a significant decrease in blood glucose levels of 67.98% and 60.30%, respectively. lose weight and improve dyslipemia to a significant degree. Research conducted by Sameni et al. (2016) showed the results that Iranian propolis extract given for 6 weeks on day 40 with consistency showed an weight gain on test animals compared to diabetic control rats without propolis treatment, decreased GMB thickness at both doses of 100 (0.49µm ± 0.05 µm) and 200 mg/kg (0.47µm ± 0.04µm) compared to control rats not treated with propolis 67.98% and significantly reduced blood glucose levels at doses of 100 and 200mg/kg compared to control rats without propolis. The administration of honey bee propolis to experimental animals is described in Table 1.

Table 1. Effects of propolis administration in animal models of type 1 diabetes mellitus

Focus of Research	Mechanism	Conclusion
Administration of propolis to diabetic rats to increase lymphocyte proliferative capacity and chemotaxis by reviewing changes lipid profiles, proinflammatory cytokines, and oxidative stress (Al Ghamdi et al. 2015)	a. Gain weight b. Lowering blood glucose levels c. Reducing the level of oxidative reactions (ROS) d. Reducing levels of IL-β and TNF-α e. Increase insulin levels f. Lower cholesterol levels	Propolis was significantly ($P < 0.05$) returned plasma cytokines, ROS levels and lipid profiles to near normal levels in diabetic mice.
Administration of Propolis from Nigeria in monitoring blood glucose	a. Lowering blood glucose levels b. Decreased plasma HbA1c levels	Treatment of diabetic rats with Nigerian propolis has activities decrease to hypoglycemic,

levels, glycated hemoglobin A1c, lipoprotein in a rat diabetes model (Oladayo 2016)	c. Lowering the VLDL serum level d. Increase HDL levels	antihyperlipidemic, and HbA1c.
Renal histopathological changes in a rat model of type 1 diabetes mellitus after administration of propolis extract (Sameni et al. 2016)	a. Inhibits weight loss b. Lowering blood glucose levels c. Increases SOD and GPx levels d. Reduces GBM thickness and glomerular area	Administration of Iranian propolis enhance antioxidant and histopathological levels in rat kidney
Changes in the content of antioxidant phenolic compounds and antidiabetic effects after administration of Nyambaka propolis extract (Balingui et al. 2021)	a. Lowering blood glucose levels b. Gain weight	Giving nyambaka propolis to test animals of type 1 diabetes mellitus model can reduce oxidative stress, hyperglycemia and increase body weight

Diabetes mellitus is characterized by hyperglycemia and disturbances in the metabolism of fats, carbohydrates, and proteins which correlate with the action of insulin. Several antidiabetic mecahnism was showed in Table 2. In type 1 diabetes mellitus, long-term inflammation caused by damage to pancreatic cells is observed with a decrease in the function of the immune response due to enhance levels of IL-6, IL-1β, and TNF- levels. Several studies have stated that there is an increase in the expression of cytokines in vitro which can stimulate bone resorption in diabetics. These cytokines include proinflammatory mediators such as IL-1β, TNF, IL-6 and prostaglandin E2. IL-1β, TNF-α and IL-6 are also important mediators in periodontal inflammation, where these mediators have important effects on glucose and lipid metabolism. TNFα is reported to interfere with lipid metabolism and become an insulin antagonist. IL-1β and IL-6 have also been shown to work as insulin antagonists. Hyperglycemia is considered as one of the main causes of diabetes complications with increased oxidative stress and toxicity. Oxidative stress occurs because of the balance between ROS (Reactive Oxygen Species).

Table 2. Antidiabetic mechanism of bee propolis metabolites

Secondary Metabolites	**Mechanism**	**References**
Flavonoid (dimethylkuradin, pinobanksin-3-O-propionate and chrysin-5,7-dimethylether) dan folifenol	Decrease blood sugar levels	(Balingui et al. 2021)
Flavonoid (nymphaeol, isonymphaeol, geranyl-naringenin)	Inhibits the activity of the glucosidase enzyme	(Shahinozzaman et al. 2018)
Flavonoid (Pinocembrin 5,7 dihidroksiflavanon)	Avoiding increases in Kidney Injury Molecule-1 (Kim-1), N-acetyl-β-D-glucosaminidase (NAG) and Neutrophil	(Granados-Pineda et al. 2018)

	Gelatinase-Associated Lipocalin (NGAL). Pinocembrin in the act of renoprotector agent in diabetic nephropathy	
Flavonoid (Chrysin 5,7 dihidroxyflavon)	Reduces renal TNF-, reduces levels of interleukin-1beta (IL-1β) and IL-6, obstruct activation of NF-kB, suppresses TGF-β, fibronectin, and collagen-IV in kidney	(Ahad et al. 2014)
Flavonoid and karotenoid	As an antioxidant and restore serum electrolytes sodium and potassium	(El Rabey, Al-Seeni, and Bakhashwain 2017)
Flavonoid (apigenin)	Apigenin in the act as antioxidant, anti-apoptosis, anti-inflammation and fibrosis reduction through suppression of the MAPK-NF-kB-TNF-α and TGF-β1-MAPK fibronectin pathways	(Malik et al. 2017)
Flavonoid (quercetin dan naringenin)	It can increase the activity of liver glucokinase enzymes, liver glucose-6-phosphatase enzymes and Phosphoenolpyruvate Carboxykinase (PEPCK)	(Rivera-Yañez et al. 2018)

Based on the data that has been collected, research conducted using animal models that are pathologically made to suffer from type 1 diabetes mellitus. The induction used is Streptozotocin (STZ) and alloxan of these two substance is a material that is often used to induce experimental animals to develop diabetes mellitus (Husna et al. 2019). STZ is a synthetic derivative of nitrosourea glucopyranose fermented by Streptomyces achromogenes which includes a broad spectrum anti-tumor antibiotic (Harijanto and Dewajanti 2017). STZ is cytotoxic to pancreatic cells. STZ also causes heart and adipose tissue destruction and enhanced oxidative stress, inflammation and endothelial dysfunction. While alloxan is a hydrophilic chemical compound that is unstable and toxic to the liver and kidneys, then at the specified dose it can cause particular destruction of pancreatic beta cells. Alloxan is gained the uric acid oxidation nitric acid (Saputra, Suartha, and Dharmayudha 2018).

Propolis is a lipophilic material, unsweetened and solid at room temperature and becomes soft, flexible and sticky at high temperature, because of waxy properties and characteristics, bees use this substance to build and restore their hives (Samadi et al. 2017). Propolis has very varied colors such as red, green, brown and black (Anjum et al. 2019). Propolis has a composition that varies depending on the region of origin and the plant sources from which they are taken. More than 500 compounds have been identified,

including flavonoids, phenylpropanoids, terpenoids, lignans, coumarins and other derivatives (Huang et al. 2014). Biological activities in propolis is related to the quantity of flavonoids and phenols in charge for its antioxidant capacity where it is said that the pharmacological activity of an extract depends on the level of active compounds contained, the greater the compound content, the higher the activity (Hernández Zarate et al. 2018).

Antioxidants are compounds that have the ability to neutralize and fight free radicals so that they have an important role to protect body cells from excess free radicals. There are several antioxidant defense mechanisms from the body to fight the effects of free radicals, namely SOD, CAT, and GPx compounds. In diabetic, high blood glucose levels can stopped antioxidant enzymes activities such as SOD, CAT, and GPx through protein glycation, resulting in oxidative stress (Stephen Irudayaraj et al. 2012). Based on previous research on the antioxidant ability of propolis that has been carried out, among others, in research (Rivera-Yañez et al. 2018) it is said that the chihuahua propolis extract, Mexico has a good antioxidant capacity of (SA50 of 15.75 g/mL and has a phenol content of as much as 31.4% and 6.2% flavonoids.In a study (Ozdal et al. 2019). Turkish propolis samples had antioxidant capacities varying between using DPPH method (1370.6 ± 198 mg TE/100 g and 6332.9 ± 114 mg TE/ 100 g) and using the CUPRAC method (2461.6 ± 278 mg TE/100 g and 8580.3 ± 234 mg TE/100 g). The mechanism of antioxidant activity of propolis is caused by phenolic compounds gave hydrogen ions to radicals to cover cells due to oxidation also food storage from oxidation reaction and poisoning propolis has ability to eliminate free radicals, which are the origin of lipids, nucleic acids and protein oxidation (Oldoni et al. 2015).

Propolis is also rich in flavonoids such as naringin, pinocembrin, naringenin, acacetin, quercetin, chrysin and luteolin. In addition, a study (Tanvir et al. 2019). using ethanol extract in Bangladeshi propolis identified compounds including tannin acid, gallic acid, catechins, pyrogallol, naringin, quercetin and many more. Flavonoids as one of the largest groups of natural phenolic compounds in plants has contribution on several activity (Parwata 2016). Flavonoids content in propolis are strong antioxidants, then able to counteract free radicals thereby cover cell membranes against lipid peroxidation. The mechanism of action is by donating hydrogen atoms to free radicals quickly and turning them into stable forms. Then there is a reduction in ROS in the pancreas (Ridwan, Sari, and Putra 2015). Flavonoids are excellent antioxidants and have been shown to reduce the oxidation of bad cholesterol (Low Density Lipoprotein), which is the cause of cardiovascular disease (Gülçin et al. 2010). Flavonoids are also protective against damage to pancreatic cells as insulin-producing cells and can increase insulin sensitivity.

Based on data that has been collected from other studies, it was found that the metabolite compounds contained in bee propolis have antidiabetic activity. Flavonoid compounds such as Chrysin reduce renal TNF-, reduce levels of IL-1β and IL-6, inhibit activation of Nuclear factor-kB (NF-kB), suppress Transforming Growth Factor (TGF-β), fibronectin, and collagen-IV. In a study conducted by (Ahad et al. 2014) that chrysin has an effect on antidiabetic nephropathy and as an anti-diabetic agent by improving kidney function parameters (BUN, serum creatinine, proteinuria and creatinine) and increasing antioxidants in the kidneys. It is said in the research of Malik et al, 2017 (Malik et al. 2017) apigeninin has activity as oxidative stress reduction, anti-apoptosis, reduce inflammation and fibrosis through suppress of MAPK-NF-kB-TNF-α and TGF-β1-MAPK fibronectin pathways so that apigenin has reaction to reduce nephropathy. Quercetin and naringenin contained in propolis have hypoglycemic and antioxidant activity.

CONCLUSION

The results of several articles that have been reviewed in this literature study showed that the administration of honey-producing bee propolis extract in Model type 1 diabetes mellitus test animals had activity in reducing levels of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), prevents inflammatory process in diabetes and has hypoglycemic activity caused by the activity of compounds contained in propolis

CONFLICT OF INTEREST

The authors declare there is no conflict of interest

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