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Research Article

LITERATURE REVIEW: ANTIDIABETIC ACTIVITY OF HONEY

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ABSTRACT

Objective: The aim of this study is to determine the antidiabetic activity of honey for people with Type 2 diabetes mellitus (T2DM) by looking at its effect on glycemic response, glycemic control, and its synergistic combination with antidiabetic drugs.

Methods: The literature review starts from problem identification, data collecting, sorting the obtained data, reading, and analyzing, finally, compiling it into a systematic review.

Results: The results show that honey has antidiabetic potential for people with T2DM as indicated by resulting good glycemic response and its combination with antidiabetic drugs results in positive glycemic control.

Conclusion: Honey possesses antidiabetic activity that could make it as an ideal supplementation for people with T2DM by helping them to achieve the ideal glycemic control and avoid further diabetic complications.

Keywords: Antioxidant, Antidiabetic, Type 2 diabetes mellitus, Hyperglycemia, Honey.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) starts when the body cells are unable to fully respond the insulin (insulin resistance), and during the state of insulin resistance, this hormone becomes ineffective, urging the body to continue producing insulin which results in damage to the pancreatic cells, because they work surpassing the limit to meet the demand, eventually lead to a decrease in the amount of insulin (insulin deficit) [1]. Insulin deficit or the inability of cells to respond to insulin causes high blood glucose levels (hyperglycemia) which are a clinical indicator of diabetes. The multifactorial and heterogeneous etiopathology cause the high cost of treatment and currently available antidiabetic drugs are still far from satisfactory, so many diabetics switch to using CAM (complementary and alternative medicine) [2]. This has sparked off more interest in research investigating the health benefits of herbs and natural products, including honey for the care and treatment of DM [3].

Carbohydrates are the main component of honey; about 95% of the dry weight of honey, in addition to carbohydrates, other compounds contained in honey include organic acids, proteins, amino acids, minerals, polyphenols, vitamins, and aroma compounds [4]. Honey has many therapeutic effects and has been used in various medicine by human civilization since ancient times. Some of the therapeutic effects include antibacterial [5,6], antiviral [7,8], antifungal [9,10], anti-inflammatory [11,12], and antitumor [13,14]. Most of the therapeutic effects that honey has can be used with various phytochemical compounds, where this variation is due to the botanical source used, namely, monofloral (from a single flower source), or multifloral (from various floral sources) [15].

Studies that aim to determine the potential of honey as a product with antidiabetic effects are increasingly being carried out both *in vitro* and *in vivo* model. The results of study conducted by Erejuwa *et al.* [16] showed that administration of honey at doses of 1 and 2 g/kg bw/day for 4 weeks to male Wistar rats with Alloxan-induced diabetes significantly reduced fasting blood glucose (FBG) and coronary risk index (CRI). Another antidiabetic activity of honey was demonstrated by study conducted by Ali *et al.* [17] on the inhibition of the activity of alpha-amylase and alpha-glucosidase enzymes by several honeys from various botanical sources, the results obtained a positive effect between the amount of flavonoid and phenolic components of honey on the inhibitory activity of the alpha-amylase and alpha-glucosidase enzymes. These studies show the antidiabetic potential of honey which can be attributed to the compounds in it.

METHODS

The literature review starts from problem identification, data collecting, sorting the obtained data, reading, and analyzing, finally, compiling it into a systematic review. The method is mainly divided into two stages; The first stage is related to the data collecting, consisting of: Problem identification, determining library sources based on eligibility criteria with inclusion or exclusion criteria, data collecting, and sorting based on the suitability of the literature with the topics discussed. The second stage is processing the data that have passed the sorting process, consisting of: Data analysis and interpretation and confirmation. Data that have been confirmed will be included in the review, while unconfirmed data will be excluded from the study.

RESULTS AND DISCUSSION

Glycemic response of honey

The appearance of sugar in the blood after meal – the glycemic response (GR) – is a normal physiological event that depends on the rate at which glucose enters the blood circulation, the amount absorbed, the rate at which it is lost from the circulation by tissues, uptake, and hepatic regulation of glucose release [18]. Carbohydrate-containing foods have various effects on GR, with some foods causing a rapid rise followed by a rapid decrease in blood sugar concentration, while others show a prolonged rise and a slow decline [19].

The glycemic index (GI) provides information about the GR that may occur when a person consumes a certain amount of food that contains a fixed amount of carbohydrates (usually 50 g), foods are classified into three categories based on its GI, low (GI 55), moderate (GI 56-69), and high (GI 70) [19]. GI is an indicator of foods containing carbohydrates, where foods with low GI are absorbed more slowly in the digestive tract, fructose-rich honey varieties are considered to be an alternative to high GI sweeteners in the dietary management of people with diabetes and cardiovascular disease [20]. Honey is a sweet substance with a relatively low glycemic index (GI), making it ideal as a sugar substitute. Table 1 summarizes the clinical studies results of honey administration on glycemic response on several subjects with various condition.

Research conducted by Ahmad *et al*. [21] subjects who were given D-glucose experienced a sharp drop in blood sugar close to the level, where a person could experience symptoms of hypoglycemia; on the other hand, the sugar levels of subjects who were given natural honey did not overcome the hypoglycemic condition and showed a higher rebound (back to baseline) blood glucose levels rapidly, this indicates that the sugar in honey is metabolized differently from glucose. Fructose is the main carbohydrate in honey and contributes to its sweetness. Research conducted by Deibert *et al*. [20] on six types of honey showed a negative correlation between the glycemic index with total fructose and in honey, indicating that fructose is one of the components in honey that is responsible for the low glycemic index of honey.

Fructose does not elevate blood sugar levels drastically because it has a different absorption and metabolism mechanism than glucose. The inactive transport process causes fructose to be absorbed only limitedly as needed so that excess fructose will remain in the intestinal lumen until the body needs it again or become a substrate for bacteria in the intestine [25]. The absorbed fructose is transported to the liver, wherein the liver will convert 29–54% fructose into an intermediate product of glycolysis (glyceraldehyde-3-phosphate) which can enter the next glycolysis metabolic process, just like glucose which will be converted into pyruvic acid later. This process does not involve the role of insulin at all [26].

Honey supplementation (by its fructose) could potentially increase glucose metabolism, glycogen synthesis and storage in the liver in either diabetic rodent models or humans [27]. This will result in improved glycemic control in patients with T2DM. Studies have also shown that administration of honey ameliorates hepatic oxidative stress and produces a hepatoprotective effect [28]. This antioxidant and hepatoprotective effect may be beneficial for the liver, especially in T2DM, because it increases the efficiency of the liver in metabolizing sugar.

Honey and its effect on glycemic control

There is evidence relating hyperglycemia and the development of secondary complications, suggesting that oxidative stress may play an important role in the etiology of diabetic complications [29]. Lifestyle managements, including medical nutrition therapy (MNT), physical activity, weight loss, and ending smoking and psychological support are fundamental aspects of the treatment of T2DM. Good glycemic control results in a significant reduction in risk and prevents the onset and development of microvascular complications [19].

There has been quite number of evidence of animal studies showing a positive effect of honey on blood sugar levels and glycemic control [30-32], although some clinical studies resulted in statistically insignificant changes, but does not rule out the possibility that clinically and statistically honey can bring significant changes for diabetics when used for a longer period of time. Table 2 outlines the clinical studies results of honey administration on subjects' glycemic control after four weeks or more [33].

Research conducted by Sadeghi *et al*. [38] showed a higher increase in blood sugar levels in T2DM patients who added 50 g of milk vetch honey to their diet after a weight maintenance diet for 2 weeks compared to T2DM patients who stopped consuming honey and then went on a weight maintenance diet for 2 weeks (controls), but at the same time, there was a more significant reduction in body weight and waist circumference than the control. Almost similar results also occurred in a study conducted by Farkla *et al*. [35] on healthy girls with obesity, where there is no decrease in blood sugar levels, but there is a significant decrease in body mass index. This occurrence may be caused by one of the flavonoid content in honey, luteolin.

Research conducted by Kwon *et al*. [39] in obese mice, administration of luteolin increased lipolysis, fatty acid (FA) oxidation, and tricarboxylic acid cycling, which could contribute to adiposity (body fat deposits) reduction and significantly reduce the weight of all white adipose tissue depots. The marked increase in hepatic steatosis and decreased adiposity in luteolin-treated mice demonstrated normalization of plasma glucose and insulin levels which are a sign of increased insulin sensitivity. Another study conducted by Aziz *et al*. [31] on diabetic rats proved that supplementation of stingless bee honey reduced levels of IL-1β and TNF-α in pancreatic islets of Langerhans indicating reduced pancreatic inflammation which leads organ to recover.

The results of clinical study of the antidiabetic activity of honey are still controversial: The difficulty of determining the right type and dose of honey, the time required for the expected results to be seen, and ethical considerations are still obstacles in conducting research antidiabetic effect of honey on humans [38]. Case report reported by Abdulrhman [40] in his 17-year observation of 38 T2DM patients (33–64 years) who consumed Clover honey (Egypt), Citrus honey (Egypt), or Ziziphus honey (Yemen and Pakistan) at a dose of 2 g/kg

Table 1: Effect of honey administration on glycemic response

Subject condition	Doses	Postprandial Blood Sugar				Unit	Reference
		0'	60'	120'	180'		
Normal (non-diabetic)	1 g/kg bw honey in 250 mL water	80.0	96.4	70.5	72.2	mg/dL	[21]
	1 g/kg bw artificial honey in 250 mL water	73.4	108.2	73.6	77.4		
	1 g/kg bbw D-glucose in 250 mL water	80.3	122.3	88.2	64.3		
	221.3 g honey in 500 mL water	92.5	100	95	-	mg/dL	[22]
	75 g glucose dilarutkan in 500 mL water (OGT solution)	90	110	90	-		
	75 g glucose+80.1 g sucrose in 500 mL water	90	125	105	-		
Prediabetic (IFG)	90 g honey in 300 mL water	100	190	155	-	mg/dL	[23]
	75 g glucose in 300 mL water	100	260	215	-		
T2DM	90 g honey in 250 mL water	141.3±39.19	244±54	230±91.9	168.9±48.26	mg/dL	[24]
	70 g dextrose in 250 mL water	145.2±39.7	331±62.4	342.6±65.8	310.6±59		
	30 g honey in 250 mL water	127±23.5	185±16.2	138±27.11	112±11.5	mg/dL	
	30 g sucrose in 250 mL water	128±30.6	210±25.5	160±18.6	130±21.7		

T2DM: Type 2 diabetes mellitus

Table 2: Effect of honey administration on glycemic control

Subject condition	Duration	Honey dose	FBG		Unit	Reference
			Before	After		
Normal (non-diabetic)	4 weeks	1.2 g honey/kg wb/day in 250 mL water	100±6.46	95.8±6.25	mg/dL	[34]
	30 days	70 g/hari dilarutkan dalam 250 mL air	96.2±44.2	92.2±39.2	mg/dL	[33]
Normal and obese	6 months	15 g/day	82.27±1.30	82.30±2.81	mg/dL	[35]
Prediabetic (IFG)	30 days	30 g/day	6.33±1.36	6.33±1.14	mmol/L	[36]
		Control	6.26±0.99	6.39±1.08		
T2DM	8 weeks	1 g/kg wb/day and increase 0.5 g/kg bb/day every 2 weeks	153.3±43.9	124.3±37.5	mg/dL	[37]
		Contol	135.9±44.7	131.9±45.5		
T2DM	2×4 weeks	50 g honey/day → (1 month break) → weight maintanance diet	129.04±35.87	134.59±34.01	mg/dL	[38]
		Weight maintanance diet → (1 month break) → 50 g honey/day	134.69±45.45	142.65±40.45		

FBG: Fasting blood glucose, T2DM: Type 2 diabetes mellitus, IFG: Impaired fasting glucose

Table 3: Effect of honey and antidiabetic drugs on blood sugar

Animal model (diabetes induction)	Duration	Dose	FBG	Unit	Reference
Male Sprague-Dawley rat, 12–14 weeks old (Streptozotocin)	4 weeks	1g/kg bw/day honey	8.8±5.8	mmol/L	[43]
		0.6 mg/kg bw/day Glibenclamide +100 mg/kg bw/day Metformin	7.9±6.5		
		0.6 mg/kg bw/day Glibenclamide+ 100 mg/kg bw/dayMetformin+1 g/kg bw/ dayhoney	6.8±8.4		
Male Sprague-Dawley rat, 12–14 weeks old (Streptozotocin)	4 weeks	0.6 mg/kg bw/day Glibenclamde	13.9±3.4	mmol/L	[44]
		0.6 mg/kg bb/hari Glibenclamide+ 1 g/kg bw/dayhoney	8.8±2.9		
		100 mg/kg bw/dayMetformin	13.2±2.9		
		100 mg/kg bw/day Metformin+ 1 g/kg bw/day honey	9.9±3.3		
Female Sprague-Dawley rat, weighing 250–350 g (Streptozotocin)	4 weeks	1 g/kg bw/day honey	22.52±3.72	mmol/L	[45]
		1 g/kg bb/hari madu+10 IU/kg bw/day Insulin	11.48±2.77		
Male albino Wistar albino, 10–12 weeks old, weighing 150–200 g (Streptozotocin)	6 weeks	3 IU/day Insulin	121.8±3.80	Satuan mg/dL	[46]
		3 IU/day Insulin+0.5 g/kg bw/day honey	106.93±3.21		

FBG: Fasting blood glucose

bw/day without the intervention of antidiabetic drugs and other diets did not show any change in glycemic status, but the patient had never experienced hypoglycemia and had decreased cardiovascular status and patients with dyslipidemia had not previously developed macrovascular complications of coronary heart disease. Further, evaluation is needed on the use of honey whether as a sole therapeutic agent or as a complementary agent in combination with antidiabetic drugs which might increase the potential of honey in suppressing hyperglycemia and preventing the development of complications in T2DM patients.

Honey and oral antidiabetic drugs combination

Antidiabetic drugs are important in the treatment of DM, but have limitations due to side effects such as causing hypoglycemia, weight gain, secondary failure, and the inability to stop pancreatic degeneration or diabetes complications related to oxidative stress [41]. Studies have shown that DM is a progressive disorder that cannot be managed effectively with drug monotherapy alone [42]. The limited effects of available antidiabetic drugs make honey an option as a supplementation agent in the diet of people with T2DM, Table 3 summarizes several results of preclinical studies which have shown a synergistic effect between honey and antidiabetic drugs on reducing blood sugar levels in diabetic animal subjects.

The combination of Glibenclamide-Metformin with honey has an antioxidant effect that can be the right choice for people with T2DM, evidenced by research conducted by Erejuwa *et al.*, [43] where the combination of Glibenclamide-Metformin with Tualang honey resulted in significantly lower blood glucose levels than the consumption of honey alone or the combination of Glibenclamide-Metformin and showed cell recovery in the islets of Langerhans. Honey contains various agents that have antioxidant properties. Gallic acid, one of the phenolic acids found in Tualang honey (and honey in general), has been shown to inhibit apoptosis caused by glucolipotoxicity in RINm5F cells (pancreatic cell culture model), by increasing the anti-apoptotic Bcl-2 (protein which regulates mitochondrial activity related to cell death) and decreases NF-B (inflammatory complex protein), caspase (a protease enzyme that plays a role in cell death), and suppresses UCP-2 signaling (mitochondrial protein that interferes with insulin and FA regulation) [47].

Administration of Gallic acid in diabetic animal models has also been shown to increase the activity of the enzymes superoxide dismutase and catalase, both of which are normally produced by pancreatic tissue, but in diabetics, the production of these enzymes decreases due to damage to the pancreas by reactive oxygen species, Gallic acid scavenges free radicals and reduces damage pancreas tissue in diabetic rats [48]. Gallic acid can also increase insulin secretion through its transcriptional activity, where the regulation of insulin gene transcription is a very complex process that requires number of transcription factors, including PDX-1 (a transcription factor important in the development and maturation of cells) [47].

CONCLUSION

Honey did not increase nor decrease blood sugar levels drastically in normal, prediabetic, and T2DM subjects which showed that honey produced a better glycemic response compared to other types of carbohydrates/sugars. Honey could also have a better effect on glycemic control when combined with antidiabetic drugs so it might be potential to be the supplementation in diabetics' diet.

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