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Original Research Article

Synergistic Effects of Noni and Honey in Ameliorating Hyperglycemia and Oxidative Stress in Diabetic Rats

Synta Haqqul Fadlilah[1*], Rizqi Yanuar Pauzi [2], Alfi Muntafiah[1], Ghea De Silva[3]

[1]*Department of Biochemistry, Faculty of Medicine, Jenderal Soedirman University, Indonesia*
[2]*Department of Microbiology, Faculty of Medicine, Jenderal Soedirman University, Indonesia*
[3]*Department of Internal Medicine, Faculty of Medicine, University of Jenderal Soedirman, Indonesia*

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Abstract

Background: The global prevalence of type 2 diabetes mellitus (T2DM) continues to increase, posing a significant public health challenge. T2DM is characterized by insulin resistance and is frequently associated with hyperglycemia and oxidative stress, which contribute to the development of chronic complications. Natural products, such as noni *(Morinda citrifolia)* and honey, have been individually investigated for their antidiabetic properties.

Objective: This study aimed to evaluate the combined effects of noni and honey on glycemic control, insulin sensitivity, and antioxidant activity in a diabetic rat model.

Methods: A total of 35 male Wistar rats were randomly assigned into seven groups, including a normal control, a diabetic control, and five treatment groups receiving noni fruit juice, honey, or their combinations at varying doses. Type 2 diabetes was induced using streptozotocin–nicotinamide (STZ–NA). Treatments were administered orally via gavage once daily for 28 days. Fasting blood glucose and superoxide dismutase (SOD) activity were measured using enzymatic assay methods, while serum insulin levels were determined using an enzyme-linked immunosorbent assay (ELISA).

Results: The combination of noni and honey significantly reduced fasting blood glucose levels ($p < 0.0001$), with the greatest reduction observed in the MCH3 group. Insulin levels and HOMA-β were significantly increased, whereas HOMA-IR values were significantly decreased in the treatment groups, particularly in MCH3. Additionally, SOD activity was significantly elevated, indicating an improvement in antioxidant status.

Conclusion: The combination of noni fruit juice and honey exerts synergistic hypoglycemic and antioxidant effects in a diabetic rat model, with the highest dose (MCH3) demonstrating the most pronounced therapeutic potential. These findings suggest that noni and honey may serve as promising complementary interventions for the management of T2DM and its associated metabolic complications.

Keywords: *honey; hypoglycemic activity; Morinda citrifolia (noni); oxidative stress; streptozotocin-nicotinamide induced diabetes rats.*
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INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) has emerged as a significant global health concern, with alarming statistics indicating a rising trend. According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes in 2021, a number projected to rise to 629 million by 2045.[1] In Indonesia, the situation is particularly critical. The prevalence of diabetes has seen a marked increase over the years, with

*Corresponding author:
E-mail: synta.haqqul@unsoed.ac.id
(Synta Haqqul Fadlilah)

estimates indicating that it rose from 5.7% among adults in 2007 to 10.8% in 2021. [2,3] This corresponds to an estimated 19.5 million adults living with diabetes in Indonesia in 2021. Projections suggest that if current trends continue, the prevalence could escalate to 16.09% by 2045, affecting over 40 million individuals.[4]

Type 2 DM is characterized by insulin resistance, a condition in which the body does not fully respond to the presence of the insulin hormone. This hormone is produced and secreted by β-pancreatic cells which play a role in stimulating the uptake of blood glucose into muscle and adipose cells. Glucose in the cells then undergoes a metabolic process to produce energy. When the body cannot produce or use insulin effectively, this causes high blood glucose levels, which is called hyperglycemia.[5]

Persistent hyperglycemia promotes increased oxidative stress, a condition that arises when the production of reactive oxygen species (ROS) exceeds the body's antioxidant capacity. This imbalance triggers inflammation and impairs insulin sensitivity in peripheral tissues, thereby playing a significant role in the pathogenesis of type 2 diabetes mellitus through various molecular pathways.[6,7] Hence, optimal diabetes management should encompass strategies that regulate blood glucose levels while simultaneously reducing oxidative stress.

Various treatments for diabetes, such as pharmacological agents (e.g., insulin, oral hypoglycemic drugs) and lifestyle modifications, have been available for decades. However, achieving optimal therapeutic outcomes remains challenging.[8] This has renewed interest in natural products as alternative treatment options. Among the vast array of natural products, noni (*Morinda citrifolia*) and honey have garnered considerable attention due to their long history of traditional medicinal use and growing scientific evidence supporting their health benefits. Noni, a tropical fruit commonly used in traditional Polynesian medicine, has been discovered to contain antioxidants and compounds such as scopoletin, which may enhance insulin sensitivity and lower blood glucose levels by modulating carbohydrate metabolism and minimizing oxidative stress.[9,10] Meanwhile, honey, which consists of natural sugars like fructose and glucose along with flavonoids and phenolic acids, has shown the potential to improve glycemic control by reducing inflammation and oxidative stress, while also promoting insulin activity.[11] Furthermore, the addition of honey as a natural sweetener to noni is expected to enhance the taste.

MATERIALS AND METHODS

This study was approved by the Research Ethics Commission, Jenderal Soedirman University, Purwokerto, Indonesia, based on the ethical approval letter number 037/KEPK/PE/II/2024.

Combination of Noni Fruit Juice and Honey Preparation

The noni fruits were obtained from Klaten, Yogyakarta, Indonesia, and were selected based on specific criteria: they were ripe, characterized by a yellowish-white color with soft, water-rich flesh, free from signs of rot (which would be indicated by a blackish color), pest-free, and weighing approximately 100 grams. The honey brand used was HNI Habbat, a pure honey product from PT. Herba Emas Wahidatama, Purbalingga, Central Java, Indonesia.

The noni fruits with the specified criteria were washed, peeled, and sliced. Afterward, the noni was blended into a puree using a juicer. Finally, pure honey was added in the designated amounts based on the dosage set for each treatment group.

Animals

The subjects of this study were 35 male Wistar rats aged 7-9 weeks, with weights ranging from 180 to 200 grams.[12] All animals were acclimatized for 7 days, kept at room temperature 20-25ºC, humidity 55% ± 5%, a 12-hour light-dark cycle (lights turned on at 8 am and turned off at 8 pm).[13] They were housed individually in cages and given standard Comfeed AD II feed. This standard feed contains 51% carbohydrate, 15% protein, 7% fat, and 6% crude fiber.

Induction of Type II Diabetes

Type II diabetes was induced following the method of Ghasemi et al. by using STZ-NA (streptozotocin-nicotinamide).[12] The rats were induced after overnight fasting by intraperitoneal injection of NA (110 mg/kg BW) dissolved in saline, followed by STZ (45 mg/kg body weight) dissolved in 0.1 M citrate buffer (pH 4.5) after 15 minutes. Three days after induction, rats with blood glucose levels of >250 mg/dL were classified as diabetic rats.

Grouping of Experimental Animals

The study involved a total of 35 rats, which were divided into seven groups, each consisting of five rats. The HC group (Healthy Control) served as the baseline group and did not receive any diabetes induction or treatment. The DC group (Diabetes Control) was induced with diabetes but did not receive any treatment, serving as a comparison for evaluating the effects of the interventions. The remaining five groups were all induced with diabetes and received different treatments. The MC group (*Morinda citrifolia*) was administered 0.72 mL/200g of noni fruit juice (NFJ). The H group (Honey) received 0.2 mL/200g of honey. Three combination treatment groups (MCH1, MCH2, and MCH3) were given varying doses of NFJ combined with a fixed dose of honey (0.2 mL/200g). The MCH1 group was given 0.36 mL/200g of NFJ + 0.2 mL/200g of honey, the MCH2 group was given 0.72 mL/200g of NFJ + 0.2 mL/200g of honey, and the MCH3 group was given 1.44 mL/200g of NFJ + 0.2 mL/200g of honey.

Noni fruit juice, honey, and a combination of noni fruit juice and honey were administered via gavage every day for 28 days to groups MC, H, MCH1, MCH2, and MCH3 according to their dosages. Blood glucose was measured before and after administration. At the end of the study, blood was taken under anesthesia to measure insulin and SOD.

Biochemical Analysis

Blood glucose was enzymatically analyzed using a commercial kit (*Diasys, Holzheim, Germany*). Insulin was analyzed using *FineTest® Rat INS (Insulin) ELISA Kit*. SOD was analyzed using *BioVision Superoxide Dismutase (SOD) Activity Assay Kit*. Homeostatic model assessment (HOMA) is a method for assessing insulin resistance (IR) and β-cell function (B) from basal (fasting) glucose and insulin. Original HOMA models were calculated using the formula HOMA-IR = [fasting insulin (μU/mL) x fasting glucose (mmol/L)]/22.5[14], and HOMA-B = [20 x fasting insulin (μU/mL)]/ [fasting glucose (mmol/L)-3.5][15]. A HOMA-IR below 2.0 typically indicates normal insulin sensitivity, where the body effectively uses insulin to regulate blood glucose levels. Values between 2.0 and 2.9 may suggest borderline insulin resistance, which could be a precursor to conditions like metabolic syndrome or prediabetes. Values ≥3.0 indicate significant insulin resistance, which is a hallmark of metabolic disorders such as Type 2 diabetes. HOMA-B values of 80-100% indicate normal beta cell function, 50-80% indicate mild impairment of beta cell function, and values below 50% are often considered an indication of impaired beta cell function, especially in individuals with type 2 diabetes.

Statistical Analysis

Statistical data analysis was performed using GraphPad Prism Version 8.4.0 software. Multiple t-tests were used to evaluate blood glucose levels before and after administration of noni, honey, and combinations of noni and honey. ANOVA test was used to evaluate insulin, HOMA-IR, and SOD after 28 days of noni, honey, and combinations of noni and honey administration. Dunnett's T3 multiple comparison test was used to determine the differences between groups. Tukey's multiple comparison test was used to determine the differences between groups of HOMA-IR and HOMA-B.

RESULTS

The Role of Noni and Honey in Ameliorating Hyperglycemia: Effects on Blood Glucose Level, Insulin, HOMA-IR, and HOMA-B

Table 1 showed that the administration of noni, honey, and their combinations resulted in significant changes in blood glucose levels among diabetic rats ($p < 0.0001$). All combination treatment groups (MCH1, MCH2, and MCH3) demonstrated a marked reduction in fasting blood glucose levels compared to the diabetic control group, with the greatest decrease observed in the MCH3 group (184 mg/dL). Honey alone also significantly reduced glucose levels, whereas noni alone (MC group) showed a comparatively smaller effect. No significant change was observed in the healthy control group. This indicated that both noni and honey may possess hypoglycemic properties.

After administration of noni, honey, and their combinations, insulin levels among diabetic rat groups were significantly different ($p<0.001$). The MCH3 group exhibited the highest average insulin level, reaching 538 mg/dL, among the five treatment groups. Analysis of HOMA-IR indicated borderline insulin resistance in healthy control (HC) rats, with significant resistance observed in all other groups. The MCH3 group, however, presented HOMA-IR values closest to the HC group. For HOMA-B, the healthy rats showed mild impairment of beta cell function, while other groups showed impaired beta cell function. However, the HOMA-B values in the MCH3 group were the highest among the other treatment groups, indicating better preservation of pancreatic beta-cell function (Table 2).

Table 1. Blood glucose level in rats before and after administration of noni, honey, and combinations of noni and honey

Groups	Blood Glucose (mg/dL)		Mean Diff.	95% CI	P
	Before	After			
HC	67.31±1.17	69.40±1.37[a]	-2.09	-7.060 -2.876	0,0629
DC	268.68±2.46	270.07±1.89[b]	-1.33	-6.296 - 3.640	0,3668
MC	265.88±5.32	106.56±2.32[c]	159.30	154.3 - 164.3	<0.0001
H	266.52±6.06	215.25±3.39[d]	51.27	46.30 - 56.24	<0.0001
MCH1	269.39±6.15	136.56±3.38[e]	132.80	127.9 - 137.8	<0.0001
MCH2	271.18±5.31	104.62±3.01[c]	166.55	161.6 - 171.5	<0.0001
MCH3	269.82±5.42	85.82±2.46[f]	184.00	179.0 - 189.0	<0.0001
P	0.0002	0.0023			

The values (n=5) are shown as mean±SD. The P value in each row was analyzed using Multiple t-tests, which indicates the differences in blood glucose levels within the same group before and after administration of noni, honey, and combinations of noni and honey. The P value in the last row was analyzed using One-sample t-test, which indicates the differences in blood glucose levels between the groups. Different letters in one column indicate significant difference among the groups based on Dunnett's T3 multiple comparisons test ($p<0.05$). HC= health control, DC= diabetic control, MC=diabetic rat received 0.72 mL/200g of NFJ, H= diabetic rat received 0.2 mL/200g of honey, MCH1= diabetic rat received 0.36 mL/200g of NFJ+ 0.2 mL/200g of honey, MCH2= diabetic rat received 0.72 mL/200g of NFJ+ 0.2 mL/200g of honey, MCH3=diabetic rat received 1.44 mL/200g of NFJ+ 0.2 mL/200g of honey.

The findings indicate that the combination of noni fruit juice at a dose of 1.44 mL/200g and honey at 0.2 mL/200g was the most effective treatment for lowering blood glucose, increasing insulin levels, improving insulin resistance and beta cell function in diabetic rats.

The Role of Noni and Honey in Ameliorating Oxidative Stress: Effects on SOD (Superoxide Dismutase)

The evaluation of SOD levels further underscores the antioxidant potential of noni and honey. According to Table 3, all treatment groups showed notable improvements in SOD levels, with combination therapies yielding the best results. The MCH3 group achieved SOD levels of 73.33 ± 2.64 mg/dL, closest to the healthy control (83.00 ± 3.21 mg/dL, P < 0.001). This reflects the strong antioxidative properties of noni and honey, which help mitigate oxidative stress in diabetic rats.

DISCUSSION

Noni (*Morinda citrifolia*) and honey have been widely studied separately for their antidiabetic properties.[11,16-22] This study explores their combined effects. The findings of this study indicate that noni and honey exhibit potential hypoglycemic, hypolipidemic, and antioxidant effects in a diabetic rat model. Among all treatments, the MCH3 group, which received the highest combination of noni juice (1.44 mL/200g) and honey (0.2 mL/200g), demonstrated the most significant improvements in diabetic rats. This included reductions in blood glucose, enhanced insulin levels, better insulin sensitivity, improved beta-cell function, increased SOD activity, and improved lipid profiles. The noni fruit juice dosage in this study was double that used in the research by Santoso et al.[23,] indicating its continued effectiveness in improving the measured parameters. Nevertheless, further research is needed to verify that this dosage does not lead to side effects,

Table 2. Insulin level, HOMA-IR, and HOMA-B value in rats after 28 days of noni, honey, and combinations of noni and honey administration

Groups	Insulin (mg/dL)	HOMA-IR	HOMA-B
HC	546.1 ± 4.24[a]	2.81 ± 0.06[a]	55.87 ± 13.02[a]
DC	457.9 ± 4.78[b]	9.16 ± 0.14[b]	1.67 ± 0.02[b]
MC	106.6 ± 2.32[c]	4.13 ± 0.11[c]	7.92 ± 0.43[c]
H	496.5 ± 2.48[d]	7.92 ± 0.12[d]	2.27 ± 0.05[b]
MCH1	506.5 ± 3.25[b]	5.12 ± 0.11[e]	4.70 ± 0.21[d]
MCH2	526 ± 5.59[a,c]	4.08 ± 0.14[c]	8.31 ± 0.61[c]
MCH3	538.2 ± 3.61[a]	3.42 ± 0.07[f]	15.20 ± 1.55[e]
P	<0.001	<0.0001	<0.0001

The values (n=5) are shown as mean±SD. P <0.05 indicates statistically significant data in insulin levels, HOMA-IR, and HOMA-B between groups. Different letters in one column indicate significant difference among the groups based on Dunnett's T3 multiple comparisons test (p<0.05) for insulin and Tukey's multiple comparisons test (p<0.05) for HOMA-IR and HOMA-B. HC= health control, DC= diabetic control, MC=diabetic rat received 0.72 mL/200g of NFJ, H= diabetic rat received 0.2 mL/200g of honey, MCH1= diabetic rat received 0.36 mL/200g of NFJ+ 0.2 mL/200g of honey, MCH2= diabetic rat received 0.72 mL/200g of NFJ+ 0.2 mL/200g of honey, MCH3=diabetic rat received 1.44 mL/200g of NFJ+ 0.2 mL/200g of honey.

Table 3. Superoxide Dismutase (SOD) level in rats after 28 days of noni, honey, and combinations of noni and honey administration

Groups	SOD level (%)	P
HC	83.00 ± 3.21[a]	
DC	25.00 ± 2.63[a,b]	
MC	64.00 ± 4.50[a,b]	
H	41.67 ± 24.41[ab]	0.002
MCH1	59.67 ± 4.31[bc]	
MCH2	67.00 ± 4.77[cd]	
MCH3	73.33 ± 2.64[d]	

The values (n=5) are shown as mean±SD. P <0.05 indicates statistically significant data in SOD. Different letters in one column indicate significant difference among the groups based on Dunnett's T3 multiple comparisons test (p<0.05). HC= health control, DC= diabetic control, MC=diabetic rat received 0.72 mL/200g of NFJ, H= diabetic rat received 0.2 mL/200g of honey, MCH1= diabetic rat received 0.36 mL/200g of NFJ+ 0.2 mL/200g of honey, MCH2= diabetic rat received 0.72 mL/200g of NFJ+ 0.2 mL/200g of honey, MCH3=diabetic rat received 1.44 mL/200g of NFJ+ 0.2 mL/200g of honey.

such as toxicity or hypoglycemia. Conversely, the honey dosage employed in this research was based on findings from Muntafiah et al.[24]

The combination of noni and honey demonstrates synergistic effects, enhancing their efficacy in managing hyperglycemia as evidenced by improvements in blood glucose, insulin levels, HOMA-IR, and HOMA-B in diabetic rats. Noni's therapeutic potential, particularly its impact on blood glucose, stems from its rich array of active compounds like flavonoids, iridoids, and triterpenoids. These compounds contribute to its hypoglycemic effects and protection against pancreatic cell damage.[25-27] Specifically, rutin, a prominent flavonoid in noni, acts as a secretagogue, stimulating insulin release from pancreatic beta cells and consequently lowering blood glucose.[25] Triterpenoids in noni have also been shown to alleviate hyperglycemia in animal models.[26] Qualitative phytochemical analysis of noni fruit juice by Santoso et al.[23] confirmed the presence of flavonoids, triterpenoids, as well as alkaloids, phenolics, and saponins. Further quantitative analysis by Santoso et al.[23] identified scopoletin content in noni fruit juice at 103.50 µg/mL. Scopoletin, a coumarin compound known for its notable ability to reduce blood glucose levels and enhance insulin sensitivity. Studies on diabetic rats (methylglyoxal-induced) showed scopoletin improved fasting blood glucose and oral glucose tolerance. Its mechanisms include inhibiting advanced glycation end products (AGEs) formation, activating peroxisome proliferator-activated receptor gamma (PPARγ) to boost insulin sensitivity, promoting Akt phosphorylation essential for insulin signaling, and restoring GLUT2 expression and translocation, all contributing to better glucose metabolism.[28]

Honey, a natural and largely unprocessed food[17], contains natural sugars (fructose, glucose), minerals, vitamins, antioxidants, and various bioactive compounds. Unlike refined sugar, honey has a lower glycemic index (GI) and a complex chemical composition, which supports its health benefits. Fructose in honey is thought to contribute to its ability to lower blood glucose levels by stimulating hepatic glucokinase activity and promoting glycogen storage in the liver. Additionally, honey is known to enhance insulin secretion and sensitivity while protecting pancreatic beta cells from oxidative damage.[18] Research by Erejuwa et al.[17] demonstrated that Tualang honey notably reduced fasting blood glucose in diabetic rats. These hypoglycemic effects are attributed to bioactive components like fructose, zinc, and copper, which collectively improve glucose uptake, insulin sensitivity, and glycogen storage. Such findings suggest that incorporating noni and honey into dietary regimens could be beneficial for individuals with glucose metabolism disorders.

Noni and honey also demonstrated their potential as natural antioxidants in this study, as indicated by their impact on enhanced Superoxide Dismutase (SOD) levels. SOD is a critical antioxidant enzyme that protects cells from oxidative damage by catalyzing the conversion of superoxide radicals into hydrogen peroxide and oxygen. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is a key contributor to metabolic disorders such as diabetes.[29] Noni's potent antioxidant properties are attributed to its rich content of flavonoids, iridoids, and phenolics. These compounds neutralize reactive oxygen species (ROS), which are elevated in diabetes and contribute to insulin resistance and beta-cell dysfunction. By reducing ROS, noni protects pancreatic beta cells and other tissues. Study has shown that Noni can enhance the activity of endogenous antioxidant enzymes like Superoxide Dismutase (SOD), catalase, and glutathione peroxidase, which are essential for maintaining redox balance and minimizing oxidative stress-related complications in diabetes. Additionally, the antioxidants in Noni protect against lipid peroxidation, protein oxidation, and DNA damage, extending protection to vascular endothelial cells and reducing the risk of diabetic complications such as nephropathy and retinopathy. By modulating oxidative stress, Noni indirectly enhances insulin sensitivity and glucose uptake in tissues. This improvement is crucial for glycemic control in diabetic patients.[10] The scopoletin in noni also contributes to its antioxidant effects by donating electrons to free radicals, thereby reducing oxidative stress. A study by Santoso et al. demonstrated that a combination of noni and temulawak juices significantly increased liver SOD activity and reduced malondialdehyde (MDA) levels in diabetic rats, indicating protection against oxidative stress.[30]

Honey also has potential as a powerful antioxidant, particularly in mitigating oxidative stress in diabetic conditions. It contains enzymatic and non-enzymatic antioxidants, such as catalase, flavonoids, alkaloids, polyphenols, carotenoids, vitamins, and Maillard-reaction products. These components enhance honey's ability to scavenge reactive oxygen species (ROS) and reduce oxidative damage. Honey administration significantly restored the activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione-S-transferase (GST) in diabetic rats. This restoration improves the antioxidant defense system, helping counteract oxidative stress induced by hyperglycemia. Additionally, honey reduced levels of thiobarbituric acid reactive substances (TBARS), indicating lower lipid peroxidation and decreased oxidative damage to cell membranes. Its ability to enhance Total Antioxidant Status (TAS) highlights honey’s comprehensive role in strengthening the antioxidant system. Histological analysis also revealed that honey alleviated kidney damage in diabetic rats by reducing mesangial matrix expansion and glomerular basement membrane thickening, conditions linked to oxidative damage.[22]

The combination of noni and honey exhibits synergistic antidiabetic effects by targeting multiple pathways involved in glucose regulation and oxidative stress. Bioactive compounds in noni, including

flavonoids, iridoids, triterpenoids, and scopoletin, contribute to hypoglycemic activity through stimulation of insulin secretion, protection of pancreatic β-cells, inhibition of advanced glycation end products (AGEs), activation of PPARγ, and enhancement of GLUT2 expression, thereby improving insulin sensitivity and glucose metabolism.[25-28] Concurrently, honey provides natural sugars, antioxidants, and micronutrients that support glycemic control by stimulating hepatic glucokinase activity, promoting glycogen storage, enhancing insulin secretion and sensitivity, and protecting β-cells from oxidative damage.[17,18] The complementary mechanisms of these two natural products result in a more pronounced improvement in blood glucose levels, insulin function, and antioxidant status compared to individual treatments, highlighting their synergistic therapeutic potential in diabetic conditions.

A limitation of this study is that phytochemical testing was not performed, making it impossible to detect the exact compounds found in the noni fruit or honey. Furthermore, the noni fruit used came from a wild plant, not a cultivated one, so the growth characteristics of the plant are unknown.

CONCLUSION

This study concludes that both noni and honey demonstrate promising potential in ameliorating hyperglycemia and oxidative stress within a diabetic rat model. Specifically, the combined treatment of noni juice (1.44 mL/200g) and honey (0.2 mL/200g), designated as the MCH3 group, proved to be the most effective intervention. This combination led to significant reductions in blood glucose, enhanced insulin levels, improved insulin sensitivity, better beta-cell function, and increased Superoxide Dismutase (SOD) activity in diabetic rats. These findings collectively underscore the potential health benefits of integrating noni and honey into dietary regimens, particularly for individuals susceptible to metabolic disorders like diabetes. Further research is warranted to fully elucidate the underlying mechanisms of these effects and to confirm their applicability in human populations.

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