Jurnal Biologi Tropis

Original Research Paper

The Role of Manuka Honey in Protecting Against Cochlear Hair Cell Damage Caused by Diabetes Mellitus in Rats, Assessed Through Otoacoustic Emission

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Article History
Received : July 01th, 2025
Revised : July 05th, 2025
Accepted : July 10th, 2025

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Abstract: Diabetes mellitus is an escalating public health concern worldwide, with Indonesia being one of the countries heavily affected and facing a projected increase in cases. This condition is known to cause a range of complications, including hearing loss, which is frequently observed in diabetic individuals. This study aims to investigate the potential protective effect of honey against cochlear damage induced by diabetes mellitus. This ex-vivo experimental study applied a pretest-posttest control group design. Conducted over five months at the FMIPA USU Animal Laboratory, the study involved 25 healthy adult male *Rattus norvegicus* Wistar rats (150–250 grams, aged 2–3 months). The rats were divided into three treatment groups and assessed before and after honey administration on days 0, 3, 6, 9, and 12. SNR value differences were analyzed using Repeated Measures ANOVA or the Friedman test. Administration of honey at a dose of 1 g/kg body weight was more effective in preventing the decline of SNR values in diabetic rat models compared to the 2 g/kg dose. Honey demonstrates a protective effect against cochlear hair cell damage in diabetic *Rattus norvegicus*, as evidenced by SNR values from OAE assessments.

Keywords: Antioxidant therapy, auditory function, honey, oxidative stress, OAE.

Pendahuluan

Diabetes mellitus (DM) has become a global health issue. Various epidemiological studies indicate a growing trend in the prevalence of DM worldwide. The World Health Organization (WHO) estimates that the global prevalence of DM will increase from 171 million people in the year 2000 to 366 million by 2030. Indonesia is among the top 10 countries with the highest DM cases. WHO predicts that the number of DM patients in Indonesia will rise from 8.4 million in 2000 to approximately 21.3 million by 2030. Similarly, the International Diabetes Federation (IDF) projects an increase in the number of DM patients in Indonesia from 9.1 million in 2014 to 14.1 million by 2035 (Perkeni, 2015).

Diabetes mellitus is characterized by hyperglycemia or an absolute lack of insulin function due to pancreatic beta-cell damage (Type 1 DM) and a relative deficiency due to ineffective insulin utilization (Type 2 DM) [Perkeni, 2015; Pieme eet al., 2017). DM can lead to complications in the eye, kidney, cranial nerves, ears, and vascular system. In the auditory system, DM can cause atrophy of the spiral ganglion, degeneration of the myelin sheath of the vestibulocochlear nerve, a reduction in the number of nerve fibres in the spiral lamina, and thickening of the capillary walls in the stria vascularis (Malucelli et al., 2012).

Study by Agarwal, 67.5% of DM patients experienced sensorineural hearing loss. Some patients reported symptoms such as vertigo and tinnitus. Hearing impairment is typically bilateral, progressive, and affects

high frequencies. These alterations are linked to cochlear damage and include thickening of the stria vascularis, atrophy of the stria vascularis, and a decrease in outer hair cells (Agarwal et al., 2013). Another study by Sachdeva found that 33.7% of DM patients had sensorineural hearing loss (Sachdeva et al., 2018).

Being an endocrine condition, diabetes mellitus is also linked to a number of metabolic abnormalities, such as elevated oxidative stress and hyperglycemia. The development of DM complications, both microvascular and cardiovascular, is significantly influenced by oxidative stress. Some of the mechanisms involving oxidative stress in DM patients include tissue changes, auto-oxidants as byproducts of glycosylation, oxygen free radicals generated by glycosylation, and/or the activation of the antioxidant defense system (Pieme et al., 2017).

Both radical and non-radical species that function as intermediate oxygen compounds are known as reactive oxygen species (ROS). ROS include both non-radicals (hydrogen peroxide and hypochlorite) and free radicals (superoxide, hydroxyl radicals, alkoxyl, and peroxyl). Atoms or molecules with one or more unpaired electrons in their outer orbit are unstable and are known as free radicals. Free radicals take electrons from other molecules in an effort to stabilize themselves. Under typical circumstances, the production of ROS and antioxidant activity are in equilibrium. Damage to biological components may result from oxidative stress, which happens when this equilibrium is upset (Chong et al., 2014).

Honey is a sweet, viscous, and fragrant meal made up of several ingredients. Sugars make up the majority of it, which helps to explain its primary characteristic sweetness. The majority of honey's carbohydrates are monosaccharides, with fructose predominating over glucose. The third most prevalent monosaccharide in honey is sucrose. Maltose, isomaltose, nigerose, turanose, and maltulose are other disaccharides that are found in extremely minute levels. Honey's sugars and other ingredients may alter when it is being stored. Some sugar breakdown products, such as 2-acetylfuran, isomaltol, 3,5-dihydroxy-2-methyl-5,6-dihydropyran-4-one, and maltol, are generated when subjected to heat in the presence of amino acids, contributing to changes in the colour, taste, and scent of honey. Honey is antibacterial and anti-inflammatory, excellent for wound healing and tissue regeneration. One key component in honey is flavonoids and polyphenols, which also function as antioxidants (Martinotti et al., 2018; Eteraf-Oskouei et al., 2013).

A weak acoustic signal from the outer hair cells in the cochlea, known as an otoacoustic emission (OAE), is used to evaluate the micromechanics of outer hair cells and cochlear function. Hair cells are important for the functional status of hearing because they are indirectly related to the functional status of inner hair cells. The examination can be measured at the external acoustic meatus as a reflection of the auditory processes occurring in the cochlea. In DM patients, OAE measurement values decrease functionally, particularly at high frequencies (Paluru et al., 2016). This study aims to determine the role of honey in cochlear hair cell damage in *Rattus norvegicus* DM models, as assessed based on the signal-to-noise ratio (SNR) values using OAE examination.

Bahan dan Metode

Type and Research Design

This study is an ex vivo laboratory experimental research with a pretest-posttest control group design to determine the role of honey in cochlear damage in *Rattus norvegicus* DM models based on Signal-to-Noise Ratio (SNR) values using otoacoustic emissions (OAE) examination. Each experimental unit was measured for the variable, specifically the SNR value, before and after honey administration on days 0, 3, 6, 9, and 12 (Lubis & Haryuna, 2022). Sample collection was conducted randomly, using a control group as a comparator.

Research Location and Time

This study was conducted over five months at the Animal Laboratory/Animal House, Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Sumatera Utara (USU). The research process included preparing materials and equipment, treatment, examination, and report compilation.

Research Sample

The sample in this study consisted of 25 male *Rattus norvegicus* Wistar strain white rats, which were healthy, in adulthood (2–3 months old), and weighing between 150–250 grams. The Federer formula determined the sample size and divided it into three treatment groups. After adapting to the laboratory cage environment for 14×24 hours, the treatment was administered according to the planned groups. The treatment involved inducing diabetes mellitus (DM) in the rats, characterized by blood glucose levels (BGL) >200 mg/dL (Mishra et al., 2020. The administered honey doses were 2 g/kgBW per rat and 1 g/kgBW per rat (Erejuwa et al., 2016).

Sample Grouping

This study involved 25 rats randomly divided into five treatment groups. All samples underwent intraperitoneal injections of Alloxan at a dose of 150 mg/kgBW per rat (Mishra et al., 2020; Luka et al., 2013). The first group (K1) was the control group, consisting of DM model rats not given honey. The second group (K2) consisted of DM model rats that received honey from day 0 at a dose of 2 g/kgBW per rat. The third group (K3) consisted of DM model rats that received honey from day 0 at a dose of 1 g/kgBW per rat. Each treatment group received honey until day 12. This study aimed to evaluate the effects of honey on the prevention and treatment of diabetes mellitus in rats.

Research Procedure

Before conducting the study, the research proposal was submitted to the Ethics Committee of Universitas Sumatera Utara to ensure that all procedures in this study met ethical standards and received ethical clearance and approval. All white rats were placed in plastic cages measuring 40×25×15 cm, with a bedding layer of approximately 0.5 cm thick sawdust, and were provided with food and water containers. The temperature was maintained at 25°C with humidity levels ranging from 40–70%. The rats were exposed to sufficient light and had free access to adequate food and water throughout the study. After adapting to the environment for two weeks, the animals were anaesthetized using Ketamine Hydrochloride (HameIn Pharmaceutical, Germany) at a dose of 50 mg/kgBW (Babisnka et al., 2017) via intraperitoneal injection. Subsequently, an otoscopic examination (Riester, Germany) was performed to ensure that the ear canals were clean and that the tympanic membrane was not abnormal.

An otoacoustic emission (OAE) examination (Grason-Stadler Corti, USA) was then conducted by inserting a probe into both the right and left ears, ensuring it fit properly into the rats' ear canals. OAE assessments were performed at frequencies ranging from 1.5 to 6 kHz. To induce diabetes mellitus (DM), the test animals were injected with Alloxan Monohydrate (Sigma, Indonesia) at a dose of 150 mg/kgBW using a 28G 1 cc syringe (One Med, Germany) via intraperitoneal injection. Blood glucose levels were measured 48 hours later using a blood glucose meter (Autocheck, Germany). A rat was considered diabetic if its blood glucose level (BGL) exceeded 200 mg/dL.

Honey (Manuka Health, New Zealand) was administered orally using a gavage tube after being diluted with distilled water in a 1:1 ratio. The honey dose was 2 g/kgBW per rat for groups 2, while groups 3 received 1 g/kgBW per rat. OAE examinations were conducted for each group on days 0, 3, 6, 9, and 12 at frequencies ranging from 1.5 to 6 kHz. The evaluated variable was the signal-to-noise ratio (SNR). An SNR value was considered normal if SNR $\geq$ 3 (pass), whereas an SNR < 3 (refer) indicated the presence of hearing impairment (Ceylan et al., 2019). Data obtained before and after DM induction were statistically analyzed using SPSS (Statistical Package for the Social Sciences).

Statistical Analysis

If the data were normally distributed, Repeated Measures ANOVA was used to analyse whether there were differences in SNR values within each research group. If the data were not normally distributed, the Friedman test was applied. One-way ANOVA was used to analyse whether there were differences in SNR changes between treatment groups, and if the data were normally distributed. If the data were not normally distributed, the Kruskal-Wallis test was applied.

Result & Discussion

This study investigated a total of 25 subjects. The subjects were healthy adult male Rattus norvegicus (Wistar strain), aged 2–3 months, and weighed between 150–250 grams.

Control Group (K1)

Table 1 shows that at a frequency of 3 kHz, the highest SNR value was observed on day 6, with a mean of 15.8 ± 10.66 dB, and it progressively decreased until day 12, reaching the lowest value with a mean SNR of 1.5 ± 0.84 dB. Using the Repeated Measures ANOVA test, it was concluded that there was a significant difference in SNR values (p = 0.012) in the control group.

Table 1 shows that at a frequency of 4 kHz, the highest SNR value was observed on day 0, with a mean of 11,80±4,09dB, and it progressively decreased until day 12, reaching the lowest value with a mean SNR of 2.4 ± 1.82 dB. Using the Repeated Measures ANOVA test, it was concluded that there was a significant difference in SNR values (p = 0.003) in the control group.

Table 1. Differences in SNR on Day 0, Day 3, Day 6, Day 9, and Day 12 in the Control Group (K1)

Freq.	Observation Time, Day-					p
	0	3	6	9	12	
1,5 KHz	6,80±3,11	4±0,71	3,6±21,9	5±4,47	1,7±2,17	0,076[a]
2 KHz	8,20±4,76	2,8±1,82	2,6±1,95	2,2±1,67	0 (0-3)	0,122[b]
3 KHz	13,60±4,56	13,4±3,85	12,8±10,66	5,2±2,78	1,5±0,84	0,012[a]
4 KHz	11,80±4,09	10,2±4,55	6,4±4,04	6,4±3,85	2,4±1,82	0,003[a]
5 KHz	11±5,12	8,2±6,72	8 (3-8)	3,2±3,49	0 (0-4)	0,019[b]
6 KHz	2 (1-20)	1,8±0,84	1,7 (1-2)	1,6±1,82	0 (0-4)	0,448[b]

Data are presented as mean ± SD and median (min-max)
[a]Repeated ANOVA, [b]Friedman

Table 1 shows that at a frequency of 5 kHz, the highest SNR value was observed on day 0, with a mean of 11 ± 5.12 dB, and it progressively decreased until day 12, reaching the lowest value with a median SNR of 0 dB. Using the Repeated Measures ANOVA test, it was concluded that there was a significant difference in SNR values (p = 0.019) in the control group.

Honey 2 g Group (K2)

Table 2 shows no significant differences in SNR values based on examination days for all frequencies (p > 0.05) in the K2 rats receiving 2 g of preventive honey.

Table 2. Differences in SNR on Day 0, Day 3, Day 6, Day 9, and Day 12 in the Rat Group Receiving 2 g Honey (K2)

Freq.	Observation Time, Day					p
	0	3	6	9	12	
1,5 KHz	8±3,74	8 (0-10)	7,2±2,51	4,8±3,11	4,7±4,64	0,285[a]
2 KHz	8,40±7,02	6,6±3,36	6 (0-10)	5,8±6,02	5,6±3,85	0,355[a]
3 KHz	10±11,68	8,2±2,17	6,8±2,28	6,7±2,3	6±4,85	0,569[b]
4 KHz	16 (8-41)	12,6±8,2	11,6±8,17	10,8±9,15	10 (8-28)	0,240[a]
5 KHz	18±12,51	16,2±8,79	15,4±5,86	14±6,44	12,2±6,18	0,452[b]
6 KHz	20,6±17,60	17,4±12,12	18,4±10,83	17 (3-29)	16,4±9,13	0,713[a]

Data are presented as mean ± SD and median (min-max)
[a]Friedman, [b]Repeated ANOVA

Honey 1 g Group (K3)

Table 3 shows that at a frequency of 4 KHz, the SNR value on day 0 had a mean of 6,80±2,28 dB, then reached its highest value on day 12 with a mean of 13,6±6,73dB. Using Repeated Measures ANOVA, it was concluded that there was a significant difference in SNR values (p=0.001) in Group K3 of rats that received 1 g of honey.

Table 3. Differences in SNR on Day 0, Day 3, Day 6, Day 9, and Day 12 in the Rat Group Receiving 1 g Honey (K3)

Freq.	Observation Time, Day					p
	0	3	6	9	12	
1,5 KHz	7,80±3,03	7,2±2,86	6,6±3,51	5,8±3,42	5,2±4,55	0,643[a]
2 KHz	6,80±3,11	7±1,58	6±4,58	5,4±2,41	4,2±3,42	0,214[a]
3 KHz	10,20±4,55	7,4±4,62	8 (5-29)	11 (7-34)	12,6±8,5	0,098[b]
4 KHz	10,80±2,28	9,6±3,65	9,8±4,44	10,6±7,16	15,6±6,73	0,001[a]
5 KHz	11,60±13,09	9,8±5,31	9 (1-34)	8 (2-46)	13,8±8,02	0,061[b]
6 KHz	11,8±5,10	10,6±2,79	13,2±10,09	12,2±13,74	13,6±7,16	0,052[a]

Data are presented as mean ± SD and median (min-max)
[a]Repeated ANOVA, [b]Friedman

Delta SNR Value Between Day 0 and Day 12

Table 6 shows that K3, the group of rats that received 1 g of honey, exhibited an increase in SNR value compared to the other groups, with a mean of 1.26 ± 9.82. Meanwhile, K2 had a mean SNR of -4.7 ± 6.35, which was still better than K1, where the mean value was -6.71 ± 5.28. Table 6 also shows that at frequencies of 1.5 kHz, 2 kHz, 3 kHz, 5 kHz, and 6 kHz, there were no significant differences in delta SNR values ($p > 0.05$). However, at a frequency of 4 kHz, a significant difference in SNR values was observed ($p = 0.05$).

Table 6. Delta SNR Value Between Day 0 and Day 12

Freq.	treatment group			
	K1	K2	K3	p
1,5 KHz	-5±4,61	-4±7,08	-2±6,53	0,429[a]
2 KHz	-4,1±4,95	-3,2±8,46	-2±5,73	0,354[b]
3 KHz	-12,5±4,61	-4±9,87	2±4,36	0,065[b]
4 KHz	-9,4±4,68	-6±15,47	5±5,26	0,005[b]
5 KHz	-8,2±5,87	-6,8±15,35	2,6±6,8	0,075[b]
6 KHz	-1,1±3,98	-4,2±27,75	2±17,12	0,283[b]
$\bar{X}$	-6,71±5,28	-4,7±6,35	1,26±9,82	

Data are presented as mean ± SD and median (min-max)
[a]Kruskal-Wallis test, [b]One-Way ANOVA

Discussion

Hyperglycemia is a defining feature of diabetes mellitus (DM), a worldwide health issue that can result in sensorineural hearing loss as one of its complications. Hyperglycemia in DM causes oxidative stress by producing more free radicals, which in turn causes vascular damage by activating the diacylglycerol/protein kinase C pathway and increasing the activity of the polyol pathway (Hasan et al., 2023). Hyperglycemia and hyperlipidemia are also linked to increased blood viscosity and impaired circulation. Research has indicated that inner ear disorders are frequently associated with microcirculation disturbances, especially those involving the stria vascularis. The resulting tissue ischemia and hypoxia can harm one or more neural units or hair cells (Xipeng et al., 2013).

The results of this study, as presented in Table 1, show a decrease in SNR values across all frequencies from day 0 to day 12. This decrease was statistically significant at frequencies of 3 kHz, 4 kHz, and 5 kHz ($p<0.05$). These findings suggest that diabetes mellitus (DM) may contribute to damage of cochlear hair cells, which play a crucial role in the hearing process. This damage is likely caused by oxidative stress and microvascular impairment commonly found in individuals with DM, affecting overall cochlear function.

Several previous studies have examined the impact of diabetes mellitus (DM) on cochlear hair cells in rats, one of which was conducted by Lubis et al., (2022). In that study, otoacoustic emissions (OAE) were used to assess the relative function of the cochlea and the micromechanics of outer hair cells. In a study by Gioacchini et al. [18], early cochlear changes were found in young adults with normal hearing who had type 1 DM using transient evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) tests, which revealed decreased OAE responses in subjects with type 1 DM, indicating cochlear

damage. The results showed a decrease in SNR values in diabetic rats during OAE examinations across all groups at frequencies ranging from 1.5 to 12 kHz, especially on day 12.

Honey is a natural herbal substance that has been widely proven to have beneficial effects in the field of health, such as wound healing, antimicrobial properties, and antioxidant activity that supports the healing process and protects the body from cellular damage. Numerous previous studies have explored the health benefits of honey. In one study, for example, El-Shafey (El-Shafey et al., 2015) found that honey's vitamin C and nutritional value increased antioxidant levels. Administration of honey before or after hypercholesterolemia induction dramatically boosted antioxidant enzyme activity and improved lipid profiles, making it an excellent medication for treating and guarding against coronary heart disorders. When given to male white rats (*Rattus norvegicus*, Sprague Dawley strain) at a honey dose of 0.5 mL/kg BW for four days, honey has also demonstrated notable efficacy in preventing stomach damage produced by aspirin induction at a level of 600 mg/kg BW (Tanny et al., 2024).

Manuka and Indonesian Trigona honeys have been shown to have beneficial effects on tympanic membrane re-epithelialization through their possible action on fibroblast and keratinocyte proliferation, keratinocyte growth secretion, and fibroblast development (Priyono et al., 2024). An increase in keratinocytes was positively connected with exposure to 0.04% and 0.1% Manuka honey and 0.04% Trigona honey. Forest honey has also shown antidiabetic effects in mice induced with alloxan at a dose of 42 mg/20 g BW, with a noticeable reduction in blood glucose levels (Aprianty et al., 2023). In line with this study's results, as shown in Tables 2 and 3, the groups of diabetic rats that were given honey (K2, K3) showed a milder decrease in SNR values compared to the group that did not receive honey (K1). This indicates that honey can potentially protect cochlear hair cells from damage caused by hyperglycemic conditions.

Based on the study by Erejuwa et al., (2016), it was found that honey doses of 2.0 g/kg BW and 3.0 g/kg BW did not show a significant glucose-lowering effect. Therefore, it can be concluded that the effective therapeutic dose of honey ranges between 1.0 and 2.4 g/kg BW. Considering that honey doses within this range produce similar glucose-lowering effects without additional significant benefits, a dose of 1.0 g/kg BW can be considered the optimal dose of honey.

The results of this study presented in Table 6 show that the group of rats given honey as a preventive treatment showed differences in SNR values depending on the dose administered. In the group of rats that received honey at a dose of 1 g/kg BW/rat, there was an increase in SNR with a mean delta value of 1,26 dB compared to the group that received a higher dose of 2 g/kg BW/rat, which showed a mean delta value of -4,7 dB. These findings suggest that a lower dose of honey may be more effective in protecting against cochlear damage than a higher dose.

Conclusion

The observed differences in SNR values between the control and treatment groups suggest that honey, when administered at either 1 g/kgBW or 2 g/kgBW, may help prevent cochlear damage in diabetic Rattus norvegicus models. Moreover, the findings of this study indicate that a 1 g/kgBW dose of honey offers more effective cochlear protection compared to a 2 g/kgBW dose in diabetic rats.

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