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Correlation Between Oxidant and Antioxidant Status (MDA and SOD Expression) and the Improvement of Outer Hair Cells Function Due to Curcumin Administration in Noise-Exposed Rattus Norvegicus Cochlea Assessed by DPOAE Examination

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ABSTRACT

NIHL caused by excessive noise exposed to cochlea. Curcumin is a medicine that has antioxidant effects. The purpose of this study was to look at the effect of curcumin on NIHL which was assessed with DPOAE, value and the expression of SOD and MDA. This research was conducted on 36 rats which were divided into 6 groups, group 1 was a control group, group 2 was a group receiving only noise treatment, groups 3 and 4 were the treatment group receiving curcumin after exposed to noise, groups 5 and 6 were preventive groups receiving curcumin starting from 14

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days before their get noise. The study result showed the correlation between SOD and MDA expression and DPOAE value due to curcumi*n* Administration in Noise-Exposed rats Cochlea. The conclussion of the study showed that curcumin was able to change the value of DPOAE, SOD and MDA expressions in rats exposed to noise.

Key words : Curcumin, noise, cochlea, antioxidants, superoxide dismutase

INTRODUCTION

Nowadays there is a lot of noise at work that causes workers to suffer from hearing loss due to work. Besides environmental noise also increased, this resulted in around 1-1.6 million people in western Europe or 1.1 million world population suffer from Noise Induced Hearing Loss (NIHL) every year. The UN World Health Organization estimates that 1.1 billion people in the world are at risk of suffering from NIHL because of the fallacy in listening behavior. In high and middle income countries, adolescents and young adults aged 12-35 years are exposed to excessive sound through personal audio devices and around 40% of them occur in clubs, discos and bars[1].

Noise will cause a shearing force that results in changes in the stereocilia of hair cells outside the cochlear basilar membrane and cell death will occur if the process occurs excessively[2]. Studies in animals exposed to noise showed anatomic changes occur ranging from stereocilia distortion of outer and inner hair cells to loss of cortical organs and rupture of the Reissner membrane. In general, changes in blood vessels, spirals or limb ligaments are not found. Stria vascular edema occurs a few minutes after exposure to noise and persists for several days[3]. Noise can cause Temporary Treshold Shift (TTS) or Permanent Threshold Shift (PTS). Generally, in TTS, the hearing will return to normal within 24-48 hours[4]. The cause of cortical organ damage can occur in two mechanisms, namely mechanical damage and continuous metabolic activity[1].

Many studies carried out over nearly 40 years have shown that otoaccoustic emission (OAE) is useful for determining the differential diagnosis of sensorineural hearing loss; cochlear screening of infants, toddlers and other patients that are difficult for hearing tests; assess outer hair cells in patients exposed to excessive noise, ototoxic or other progressive disease sufferers[5]. One type of OAE examination is Distortion Product Otoacoustic Emission (DPOAE), this examination is very suitable and sensitive to assess ear responses to dangerous stimuli such as toxic, trauma and cochlear degenerative processes[6].

Oxidative stress due to noise exposure damages the antioxidant defense mechanism in the cochlea so that Reactive Oxygen species (ROS), Reactive Nitrogen Species (RNS) and other free radicals are formed excessively, to overcome this

detoxification process occurs. This defense mechanism consists of enzymes and antioxidants. Enzymes such as Superoxide Dismutase (SOD) catalyze the removal of O2- to H_2O_2, Glutathione peroxidase (GPx), Glutathione reductase (GR) and Catalase (CAT)[7]. Oxygen free radicals can attack proteins, nucleic acids and lipid membranes that disrupt the normal function and integrity of cells. An increase in neurotransmitters in the brain area after exposure to noise and can persist for up to 15 days after exposure. In addition there is also an increase in Malondialdehyde (MDA) as the end result of lipid peroxidation[8] and is a marker for damage caused by free radicals[9].

In the future prevention and treatment efforts for NIHL can be increased by the use of chemoprotective agents such as antioxidants and identification of risk factors[2]. Turmeric (*Curcuma longa Linn*) is one of the most well-known herbal medicines and has many pharmacological activities such as antioxidants, anti-inflammation, anti-tumor, anti-proliferation, anti-angiogenic, anti-aging, antiprotozoa, anti-microbial, and anti-malaria[10]. Turmeric has the main active components namely *curcuminoids*, *monoterpenoids* and *sesquiterpenoids*[11]. Whereas *curcuminoids*, consisting of *curcumin*, *demethoxycurcumin* and *bisdemethoxycurcumin*[10,11].

Previous studies have shown that curcumin has the effect of preventing and treating the damage of supporting fibroblast cells and the lateral wall of the cochlea due to noise exposure with increased SOD and CAT expression[12] and decreased MDA and H_2O_2 expression[13].

This study is different from the previous studies, in this study we want to prove that curcumin is able to cause changes in oxidant and antioxidant status in hair cells / cochlear cortical organs so that the outer hair cell function improves as evidenced by DPOAE examination in rats exposed to noise.

METHODOLOGY

This study used a randomized post test only control group laboratory experimental design. This study founded by Research Institute of the Universitas Sumatera Utara under the TALENTA Research Implementation Contract of the Universitas Sumatera Utara 2018 fiscal year No: 2590 / UN.5.1.R / PPM / 2018 on March 16, 2018.

Ethical Approval

Before the study was conducted, this study approved ethical clearance from the ethics research institute of the Faculty of Medicine, Universitas Sumatera Utara with number 509 / TGL / KEPK FK USU-RSUP HAM / 2018.

The Groups of The Study

The study was conducted on 36 male *Rattus norvegicus* pure strain rats, weighing 200-300 grams and declared healthy by veterinarians. All rats were treated in a polycarbonil cage to ensure the temperature of the cage remained at 20°C-26°C with humidity around 30-70%. It is ensured that all rat receive sufficient light sources and get adequate food and drink[14].

This study was divided into 6 groups, each consisting of 6 rats. The first group is a control group without administration of curcumin and noise exposure. Group 2 is a group of rats with only noise exposure without curcumin. Group 3 and group 4 are curative groups. Group 3 is a group with noise exposure and curcumin 100 mg / day for 2 days after exposure to noise. Group 4 is a group with noise exposure and curcumin 200 mg / day for 2 days after giving noise exposure. Group 5 is a preventive group that starts with 100 mg of curcumin / day for 2 weeks followed by noise exposure and 100 mg / day of curcumin for 2 days. Group 6 is a preventive group that starts with 200 mg / day of curcumin for 2 weeks followed by noise recording given at a frequency of 1-10,000Hz with an intensity of 110 dB for 2 hours / day, for 2 days. Noise treatment is carried out by placing rats on a box (with a size of 64.5 x 45 x 40) cm made of cork coated by foam, speakers are placed attached to the roof of the box cover and a hole is made at the base of the box to measure the intensity, measurements are made at eight points where the cage will be placed with a noise difference not exceeding 1 dB using a sound level meter.

Procedures of DPOAE examination.

Examination of DPOAE using Distortion Product Otoacoustic Emissions (DPOAE) of the brand Elios Elito Otodia (Echodia Ltd., London, UK) was carried out 2 times; before the noise treatment was carried out and after 2 days of noise treatment. Before examination, rats were first anesthetized using Ketamine at a dose of 90 mg / kgBW and Xylazine at a dose of 10mg / kgBW which was injected intraperitoneally[15,16]

Procedures for Curcumin Administration

In this study, curcumin given was extracted from *Curcuma longa L* (turmeric, with certificate number 0532 / SA / V / 2016, certified by Dr. Rer. Nat. M. Yuwono, MS, Department of Pharmacy, Airlangga University) with a concentration of 16.62% ± 0.14% w / w calculated by the TLC-densitometry method. Curcumin given at a dose of 100 mg and 200 mg, which was diluted in CMC / Carboxy methyl cellulose 0.5% was given using Nasogastric Tube (NGT). After all treatments were completed, the rats were terminated by inhalation of ether and necropsing of the rat's temporal bone.

Immunohistochemistry Staining

Temporal bone taken was fixed with 10% formalin buffer solution, then by using EDTA for 4 weeks it was expected for decalcification to occur. Next, each tissue sample was prepared in a paraffin block and sliced into 4 μm thick sections and placed in a slide and then stained with hematoxylin-eosin and immunohistochemical staining. SOD staining with primary antibodies (SOD-2 (A-2) (Santa Cruz Biotechnology, Inc. cat # sc-133134)) and MDA with anti-malondialdehyde antibodies (abcam cat # ab6463) to assess SOD and MDA expression in cortical organs cochlea. The XC 10 Olympus microscope using 40x magnification was used to calculate SOD and MDA expressions using a double-blind method performed by two examiners separately (researcher and anatomist pathologist). SOD and MDA expressions were assessed by a broad score (P) and Intensity score (I) of the brown color on the cytoplasm. Intensity score: 1-3, broad score 0: 0%; 1: <10%; 2: 11% -50%; 3: 51-80%; 4:> 80% to obtain an immune-reactive score which is the product of P and I multiplication, with a value of 0-12[17].

Statistical Analyze

All data collected was analyzed statistically using the ANNOVA test to assess differences in each treatment and bivariate analysis was also performed using the Pearson test to assess the correlation between DPOAE examination with SOD and MDA expressions.

RESULT AND DISCUSSION

To get the appropriate cut of the cochlea, hematoxylin-eosin staining is done before immunohistochemical staining. A picture of cochlea with hematoxylin eosin staining can be seen in Figure 1 below.

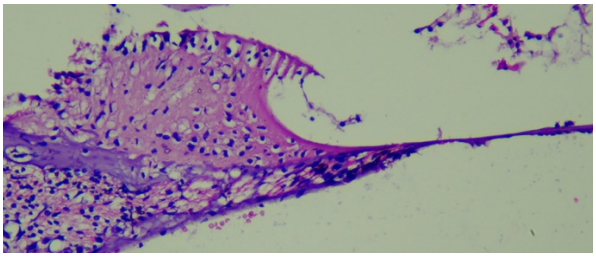

Figure 1: Figure of *Rattus norvegicus* (red arrow) cochlear cortical organ with hematoxylin-eosin staining under 400 magnification.

The SNR value of group 2, the group that received only the lowest noise of 110 dB when compared with the control group (group 1) and the group receiving curcumin (groups 3,4,5, and 6) as shown in table 1. ANOVA test found significant differences between groups (p = 0,000) as seen in table 2. Table 3 shows the significant differences between the control group (group 1) with the group that only gets noise treatment (group 2) and the group given curcumin (group 4,5 and 6) with a value of p <0.05. In this study no significant differences were found in changes in SNR values between the preventive group and between the curative groups regarding the difference in curcumin doses of 100 and 200 mg.

Table 1. Average SNR scores between groups

	N	Mean	Standard Deviation
Group 1	6	9,833	2,2923
Group 2	6	4,167	2,4147
Group 3	6	7,767	1,1759
Group 4	6	6,800	,6197
Group 5	6	6,833	,9245
Group 6	6	6,000	,4382
Total	36	6,900	2,2386

Table 2. ANOVA Test of SNR Value in Each Group

Group	Mean Difference ± Standard Deviation	p Value
Group 1	9,833 ± 2,2923	,000*
Group 2	4,167 ± 2,4147	
Group 3	7,767 ± 1,1759	
Group 4	6,800 ± 0,6197	
Group 5	6,833± 0,9245	
Group 6	6,000± 0,4382	

** Differences are statistically significant*

Table 3. Post Hoc Test Value SNR Value

		Mean difference	p Value
Group 1	Group 2	5,6667	0,000*
	Group 3	2,0667	0,206
	Group 4	3,0333	0,019*
	Group 5	3,0000	0,021*
	Group 6	3,8333	0,002*
Group 2	Group 3	-3,6000	0,004*
	Group 4	-2,6333	0,055
	Group 5	-2,6667	0,051
	Group 6	-1,8333	0,321
Group 3	Group 4	0,9667	0,877
	Group 5	0,9333	0,892
	Group 6	1,7667	0,360
Group 4	Group 5	-0,0333	1,000
	Group 6	0,8000	0,941
Group 5	Group 6	0,8333	0,930

** Differences are statistically significant*

SOD expression decreased in the group that only received noise treatment (group 2) when compared to the control group (group 1) and increased in the group with noise treatment and curcumin administration (groups 3,4,5, and 6) seen in table 4. In the figure 2 the brown color shows SOD expression where there is a decrease in the intensity of brown color in the cytoplasm of cochlear cortical organs of group 2 compared to the control group and seen an increase in the intensity of brown color in group 3,4,5, and 6 when compared to group 2. As seen in Table 5 in this study was found significant differences between groups. Table 6 shows that in this study there were significant differences between the groups that only received noise treatment, namely group 2 and all groups. In the group that given curcumin, the difference in curcumin dose in the curative group (groups 3 and 4) and the preventive group (groups 5 and 6) did not have a significant difference with a p value of <0.05.

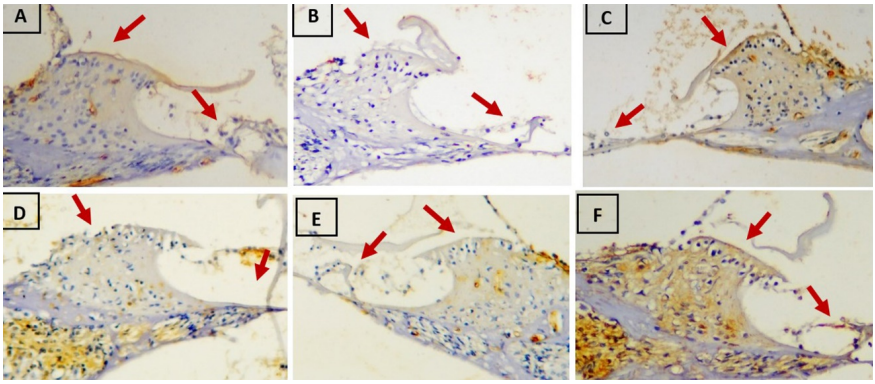

Figure 2: SOD expression in each group under 400 magnification, namely A; Group 1, B; Groups 2 and C; Group 3, D; group 4, E; group 5 and F; group 6, arrows show SOD expression in cochlear cortical organs which are marked in brown.

Table 4. Average SOD Expressions for each group

	N	Mean	Standard Deviation
Group 1	6	9,00	1,897
Group 2	6	4,00	1,897
Group 3	6	8,17	2,563
Group 4	6	9,83	2,563
Group 5	6	8,50	1,975
Group 6	6	10,00	2,449
Total	36	8,25	2,912

Table 5. ANOVA Test on SOD Expression in Each Group

Group	Mean Difference ± Standard Deviasi	p Value
Group 1	9,00 ± 1,897	,001*
Group 2	4,00 ± 1,897	
Group 3	8,17 ± 2,563	
Group 4	9,83 ± 2,563	
Group 5	8,50 ± 1,975	
Group 6	10,00 ± 2,449	

** Differences are statistically significant*

Table 6. Post Hoc Test for SOD Expression

		Mean Differnce	p Value
Group 1	Group 2	5,000	0,007*
	Group 3	0,833	0,987
	Group 4	-0,833	0,987
	Group 5	0,500	0,999
	Group 6	-1,000	0,970
Group 2	Group 3	-4,167*	0,033*
	Group 4	-5,833*	0,001*
	Group 5	-4,500*	0,018*
	Group 6	-6,000*	0,001*
Group 3	Group 4	-1,667	0,790
	Group 5	-0,333	1,000
	Group 6	-1,833	0,718
Group 4	Group 5	1,333	0,904
	Group 6	-0,167	1,000
Group 5	Group 6	-1,500	0,853

** Differences are statistically significant.*

Figure 3 shows an increase in the intensity of the brown color in the cytoplasm of the cochlear cortical organ which shows increased expression of MDA in group 2 compared to the control group. In groups 3,4,5 and 6 there was a decrease in the intensity of the brown color in the cytoplasm of the cochlear cortical organ when compared to group 2. As shown in table 7, this study found an increase in MDA expression in the group that received only noise treatment (group 2) when compared with the control group (group 1), and found a decrease in MDA expression in the group with the administration of noise and curcumin (groups 3, 4, 5 and 6) but not lower or equal to the value of MDA expression in group 1. With the ANOVA test was found a significant difference between groups as seen in table 8. In this study was found significant differences in the expression of MDA in the group that only received noise treatment (group 2) with all groups both the control group (group 1) as well as the noise and curcumin administration group (group 3,4 , 5, and 6) as shown in table 9. Differences in dose did not show significant differences either in the curative group and preventive groups.

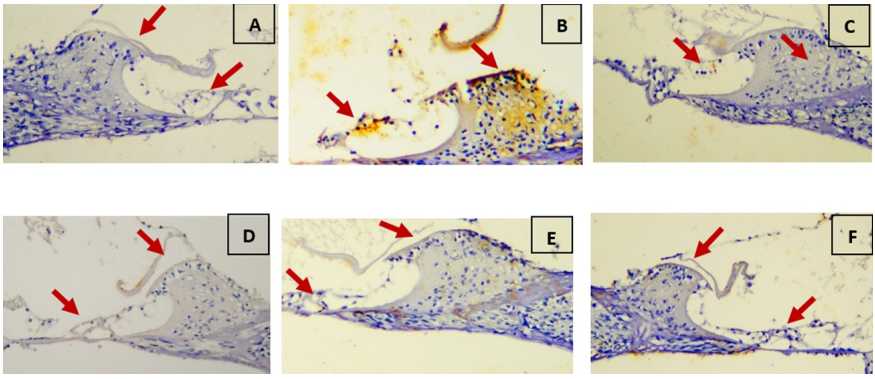

Figure 3: MDA Expressions in each group under 400 magnification, namely A; Group 1, B; Groups 2 and C; Group 3, D; group 4, E; group 5 and F; group 6, arrows show MDA expression in cochlear cortical organs which are marked in brown.

Table 7. The mean values of MDA expressions for each group

	N	Mean	Standard Deviation
Group 1	6	2,00	1,095
Group 2	6	7,33	3,670
Group 3	6	3,33	1,751
Group 4	6	3,17	1,941
Group 5	6	3,33	1,966
Group 6	6	3,17	2,317
Total	36	3,72	2,700

Table 8. ANOVA Test of MDA Expressions in Each Group

Group	Mean Difference ± Standard Deviation	p Value
Group 1	2,00 ± 1,095	,007*
Group 2	7,33 ± 3,670	
Group 3	3,33 ± 1,751	
Group 4	3,17 ± 1,941	
Group 5	3,33 ± 1,966	
Group 6	3,17 ± 2,317	

** Differences are statistically significant*

Table 9. Post Hoc Test MDA expression values

		Mean Difference	p Value
Group 1	Group 2	-5,333	0,004*
	Group 3	-1,333	0,907
	Group 4	-1,167	0,945
	Group 5	-1,333	0,907
	Group 6	-1,167	0,945
Group 2	Group 3	4,000	0,048*
	Group 4	4,167	0,036*
	Group 5	4,000	0,048*
	Group 6	4,167	0,036*
Group 3	Group 4	0,167	1,000
	Group 5	0,000	1,000
	Group 6	0,167	1,000
Group 4	Group 5	-0,167	1,000
	Group 6	0,000	1,000
Group 5	Group 6	-0,167	1,000

* *Differences are statistically significant*

All SNR values of SOD and MDA expression in each group are normally distributed so that the Pearson test can be performed on all groups. Pearson test results show there is a siginificant positive correlation between the value of SNR with SOD expression and siginificant negative correlation between the value of SNR with MDA expression in groups 2, 3, 4, 5, and 6 as shown in table 10.

Table 10. Person Correlation betweem SNR values with SOD expressions and MDA expressions of the Groups

Group		Mean ± Standard Deviation	R	p Value
Group 2	SOD	4,00 ± 1,897	0,891	0,17*
	MDA	7,33 ± 3,670	-0,816	0,48*
	SNR	4,167± 2,4147		
Group 3	SOD	8,17 ± 2,563	0,905	0,13*
	MDA	3,33 ± 1,751	-0,907	0,13*
	SNR	7,767 ± 1,1759		
Group 4	SOD	9,83 ± 2,563	0,831	0,040*
	MDA	3,17 ± 1,941	-0,865	0,026*
	SNR	6,800 ± 0,6197		
Group 5	SOD	8,50 ± 1,975	0,822	0,045*
	MDA	3,33 ± 1,966	-0,887	0,018*
	SNR	6,833± 0,9245		
Group 6	SOD	10,00 ± 2,449	0,894	0,016*
	MDA	3,17 ± 2,317	-0,867	0,025*
	SNR	6,000± 0,4382		

* *Statistically significant*

Noise exposure causes a variety of damage to the cochlea both during noise exposure and after the noise exposure is stopped so that it will ultimately affect hearing sensitivity[18]. Regular or prolonged exposure to noise can cause damage to the sensory cells and other structures gradually, which cannot be recovered, leading to PTS (Permanent Threshold Shift)[1]. Noise can cause damage to cochlear function through 7 mechanisms, namely free radical formation, mechanical damage, release of glutamate into hair cells in the cochlea, excessive stimulation of N methyl-D-aspartame receptors that cause nitric oxide release, decrease in magnesium which causes changes in intracellular activity, increased intracellular calcium activity and protein damage[19].

The formation of free radicals will cause oxidative stress. Antioxidants in general function as free radical scavenger which can repair damage caused by free radicals. Curcumin is known as an antioxidant and is reported to have free radical scavenger activity[20]. Other studies have concluded that administration of curcumin before and during paclitaxel can significantly protect the morphology and function of cochlea in pacoxitaxel-induced ototoxic rats assessed by using a light microscope and DPOAE examination to evaluate histopathology, immunohistochemistry, and hearing functional changes[21].

In this study group 2 that received noise treatment for 2 days with an intensity

of 110 dB for 2 hours the SNR value decreased compared to the control group, this shows that in group 2 there was NIHL. In groups 3, 4, 5, and 6 which are groups with the same noise treatment group as group 2 followed by administration of curcumin there was an increase in SNR value ≥ 6. In this study also found a significant difference in SNR values between group 1 and group 2, 4, 5 and 6 ($p < 0.05$) which can be interpreted that the administration of curcumin in the group with the noise treatment can increase the SNR value, this is in accordance with previous studies conducted by Yamaguchi et al who found that the administration of curcumin orally for 3 days before and each days during noise exposure significantly reduce hearing loss caused by repeated noise exposure. In that study the auditory hearing used was BERA and was found that dose of 100 mg / kgBW of curcumin was capable of partially but significantly attenuating the noise-induced elevation of the auditory threshold at 12 and 20 KHz frequencies[22].

SOD expression decreased in the noise treatment group only (group 2) when compared to the control group (group 1) and increased in the group with noise treatment and curcumin administration (groups 3,4,5, and 6). Significant differences were found between the groups that were only exposed to noise (Group 2) with the control group and the group that received noise exposure followed by the administration of curcumin (groups 3,4,5, and 6) ($p < 0.05$). This study is in accordance with research conducted by Kavakli et al who found that administration of curcumin protected spinal cord tissue from oxidative damage through a mechanism of increasing SOD enzyme activity and a decrease in MDA levels in rat animals which were subjected to spinal cord trauma and laminectomy[23]. Curcumin can increase the antioxidant status and expression of caspase-9 gene and inhibit the process of oxidative stress and lipid peroxidation in rat colon cancer tissue induced by 1,2-dimethylhydrazine. Curcumin has been shown to increase SOD and GST activity and levels of GSH, caspase-9 and DNA fragmentation and reduce the increase in MDA and NO concentrations that occur in the colon tissue[24]. This study is also in accordance with the research conducted by Meshkibav et al who found that curcumin increases the level of antioxidant enzymes such as SOD, CAT and GPx in rats with arthritis models. The study also found that the increase in MRSA levels was due to the antioxidant effect of curcumin[25].

This study found an increase in MDA expression in the group that received only noise treatment (group 2) when compared to the control group (group 1). This is in accordance with the research by Demirel et al which showed an increase in MDA levels, indicators of lipid peroxidation, as well as NO levels

and GSH-Px activity by noise exposure indicating oxidative stress which can cause various levels of damage in cells, especially through lipid peroxidation pathways[8]. In the group with noise treatment followed by administration of curcumin of group 3, 4, 5, and 6 was found a decrease in the value of MDA and found significant differences between the group that only received treatment (group 2 compared) to all groups that received noise treatment followed by administration of curcumin (groups 3,4,5, and 6). Research conducted by Zheng et al (2009) found that administration of curcumin was able to reduce MDA levels and expression of c-fos protein in the brains of rats that were damaged due to ischemic hypoxia. In this study an improvement was seen in changes in the structure and morphology of neuron cells in the cortex of the rat brain after administration of curcumin[26].

In the previous study, curcumin was found to be able to significantly increase SOD expression[11] and decrease MDA expression[12] in noise-exposed cochlear fibroblasts ($p < 0.05$). However, this study proves that curcumin can increase SOD expression and decrease MDA expression in outer cochlear hair cells in rats that are exposed to noise, causing improvement in outer hair cell function as measured by the increase of SNR values on DPOAE examination. Was also found a positive correlation between SNR values with SOD expression and negative correlations between SNR values with MDA expression in all treatment groups. Increased SOD expression and decreased MDA values led to an increase in the SNR value after administration of curcumin in groups 3,4,5, and 6. In the end this study, the results could perform as the basis of benchmarks for further studies in humans that prove the benefits of curcumin in repairing cochlear cortical organ damage which is assessed by DPOAE examination. Research by Soyalıç et al found that curcumin can protect cochlear tissue from acoustic trauma in rat. Intra-peritonial curcumin injection before and after acoustic trauma reduces cochlear hair cell damage and protects from hearing damage assessed by DPOAE, histopathological and immunohistochemical examinations[27].

This research proves the existence of Correlation between Oxidant (MDA) and Antioxidant (SOD) Status and the improvement of outer hair cell function which is assessed by DPOAE examination in the cochlea of *Rattus norvegicus* which is exposed to noise due to curcumin administration, where positive correlation was found between SOD expression and SNR value and negative correlation between MDA expression and SNR value.

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CONFLICT OF INTEREST

Nothing to declare

AUTHOR CONTRIBUTION

Design: Tengku Siti Hajar Haryuna

Acquisition of data: Reastuty

Analysis of data: Tengku Siti Hajar Haryuna and Reastuty (these authors contributed equally)

Drafting of the manuscript: Tengku Siti Hajar Haryuna and Reastuty (these authors contributed equally)

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Supervision: Tengku Siti Hajar Haryuna (this author contibuted fully)

Other (Specify): Histopatological and molecular biology expertise: Wibi Riawan

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