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The effectiveness of curcumin as a safe agent on hearing threshold improvement in patients with chronic kidney disease: a double-blind, placebo-controlled trial

Aida Doostkam[1], Kamyar Iravani[2], Leila Malekmakan[1], Ghazal Gholamabbas[1], Jamshid Roozbeh[1]✉ & Amir Soltaniesmaeili[2]

Hearing impairment in patients with chronic kidney disease (CKD), can affect the quality of life. At present, hearing dysfunction does not have an approved pharmacologic therapy. This study aimed to investigate the protective effects and possible mechanisms of curcumin as a therapeutic agent on hearing impairment in patients with chronic kidney disease. We conducted a randomized controlled trial of 40 chronic kidney disease patients not on dialysis with hearing impairment. Participants were randomly divided into two groups. One group received curcumin daily and the other received a placebo for 12 weeks. The interval between III and V waves, latency of wave V, auditory brain stem response (ABR) threshold, speech reception threshold (SRT), and speech discrimination score (SDS) were evaluated and analyzed before and after the intervention. After treatment, in the curcumin group, III–V waves interval and the latency of wave V were significantly reduced (*P* value < 0.0001), also ABR threshold was demonstrated a significant improvement (*P* value < 0.0001). In the trial group, the SDS was increased (*P* = 0.001) and the SRT was attenuated (*P* < 0.0001). We had either significant deterioration due to the course of the disease or insignificant changes in the placebo group. Daily administration of curcumin, can significantly improve hearing impairment in CKD patients. Accordingly, curcumin should be considered as a therapeutic option for treating hearing impairment in patients with chronic kidney disease.

Keywords Curcumin, Chronic kidney disease, Hearing impairment

Chronic kidney disease (CKD), as a progressive reduction in renal function, is one of the leading causes of mortality and morbidity worldwide and affects more than 800 million people in the world[1]. Due to long-standing biochemical changes and the accumulation of waste products, many organs and systems are affected in CKD patients[2]. The resultant biochemical alteration, especially in the nervous system and sensory organs, can seriously affect the quality of life in CKD patients[3]. The prevalence of CKD as a critical public health problem is rising in older people, and it can enhance morbidity and mortality and health system costs[4].

Previous studies showed an independent association between reduced kidney function and lower eGFR with hearing impairment[5–7]. The prevalence of auditory system problems is higher in CKD patients than in the general population, which can negatively affect quality of life[8].

The report of sensorineural hearing loss (SNHL) prevalence in people suffering from CKD varies significantly from country to country. A prevalence of hearing loss (between 71 and 76%) was seen in previous investigations[9].

Physiological mechanisms such as the active transport of fluid and electrolytes in the glomerulus in the kidney and stria vascularis of the cochlea are similar; therefore, the systemic metabolic, hydroelectrolytic, and

[1]Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. [2]Department of Otolaryngology, Otolaryngology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. ✉email: roozbehj@hotmail.com; roozbehj@sums.ac.ir

hormonal changes associated with chronic renal failure can affect the cochlea[10,11]. Various mechanisms have been proposed for hearing impairment in patients with CKD. Water and electrolyte homeostasis changes can affect endolymphatic fluid composition, and pressure leads to endolymphatic hydrops. Also, high-ceiling diuretics, aminoglycoside antibiotics, drug adverse effects, hemodialysis, and hereditary causes can result in hearing loss in these patients[9]. Chronic dialysis as a treatment for end-stage renal failure can also increase the odds of hearing loss; this can be due to the accumulation of amyloid materials in the cochlea. Aluminum toxicity may cause hearing impairment in chronic dialysis patients[12].

The grades of hearing impairment as recommended by the Global Burden of Disease (GBD) expert group on hearing loss as follows; Normal hearing: 0–19 dB, mild hearing loss: 20–40 dB, moderate hearing loss: 41–60 dB, severe hearing loss: 61–80 dB, profound > 81 dB[13].

Curcumin is the main ingredient of turmeric (Curcuma longa), a natural polyphenol often used in traditional herbal remedies and dietary spices. Curcumin is a strong candidate for inclusion in the treatment of CKD due to its anti-inflammatory, antioxidant, and other properties, such as lowering blood pressure, reducing proteinuria, improving cardiovascular system performance, and improving the complications of diabetic nephropathy[14,15]. As shown in various studies on the effect of curcumin in improving hearing loss and preventing deafness, it is considered that curcumin reduces oxidative damage to hair cells and neurons due to its antioxidant and anti-inflammatory effects[16–18].

Curcumin preserves mitochondrial function and prevents cell degeneration. It can enhance Nrf2 expression, reduce cleaved-caspase-3, p21, and γ-H2AX levels in cochlear tissues, and its downstream target gene Heme Oxygenase 1 (HO-1). The protective effect of curcumin is mainly achieved by activating Nrf2/HO-1 through the AKT pathway. Curcumin protects auditory hair cells by mitigating oxidative stress-related damage and reduces apoptosis and markers of cell senescence[19].

By activating the antioxidant system and anti-inflammatory effects, curcumin may reduce the symptoms and complications of chronic kidney failure, such as hearing disorders, in patients.

In one of our recent studies, curcumin significantly improved olfactory function in CKD patients.

Curcumin reduces oxidative damage to neurons and can improve the function of the olfactory nerve with effect on cell migration, axonal regeneration, re-myelination, and functional recovery[20]. So maybe curcumin can improve the function of the auditory nerve as well as the olfactory nerve. Still, until now, no study has investigated the effect of curcumin on hearing impairment in CKD patients. Therefore, the primary aim of this study was to determine whether curcumin improves hearing loss in CKD patients.

Material and methods

Study design

The current study was a prospective, double-blind, randomized clinical trial that was conducted under the supervision of Shiraz University of Medical Sciences to compare the effect of curcumin and placebo on hearing loss in chronic kidney disease patients.

Participants

At first, we conducted a cross-sectional study in CKD patients not on dialysis with age between 20 and 50 years old (to avoid age-related hearing impairment and duration of illness > 5 years). This study assessed the auditory function among CKD patients compared to the control group. We assessed auditory threshold, interval waves III and V, latency of wave V, speech reception threshold (SRT), and speech discrimination score (SDS) using the auditory brainstem evoked responses (ABRs) and aided speech audiometry tests in the studied groups.

Then we started the next study. We used the sample size formula of $n = \frac{Y^2_{1-\alpha/2}\sigma^2 + Y^2_{1-\beta}\sigma^2}{(\partial)^2}$ for the difference of means for the two groups by with 5% error, 95% confidence, and 90% power. The studied population consisted of all CKD patients visiting the Shiraz University of Medical Sciences clinics with hearing impairment in the initial evaluation (20 patients in curcumin and 20 in placebo groups, Fig. 1). The data collection was completed through interviews, examinations, and their previous records. A total of 40 cases were enrolled in the study during two years (2022–2023). The criteria for entering the study included the following: informed consent, willingness to participate in the study, a definite diagnosis of CKD by a nephrologist, a history of at least six months since the diagnosis of the disease, no mental illness, no use of other complementary medicine methods, minimum age of 18 and a maximum of 50 years, no other antioxidant treatment except nephrovit tablets (contains vitamins B1, B2, B6, B5, B12, vitamin E, ascorbic acid, biotin, zinc, nicotinamide, and folic acid). Also, an exclusion criterion was unwillingness to continue cooperation in the research.

Randomization and masking

In this study, 40 patients who met the inclusion criteria were randomly divided into two study groups (20 patients in the experimental group and 20 in the placebo group) using permutation block randomization for allocation sequence, utilizing four blocks of 4. An examiner (AD) generated the allocation sequence, enrolled participants and assigned participants to interventions, who was blind to the allocation groups.

Procedures

For all patients, before starting the study, a complete history and a full examination of the ear, throat, and nose were made by the relevant specialist and project partner, and the data collection form, which includes demographic, clinical, and laboratory information, was completed.

Each patient in the experimental group received curcumin as one 500 mg capsule daily in the morning with food. (500 mg of turmeric extract with 475 mg of curcuminoid, Karen Company). Each patient received capsules containing starch (placebo) in the placebo group for 12 weeks. The characteristics of the type and dosage of

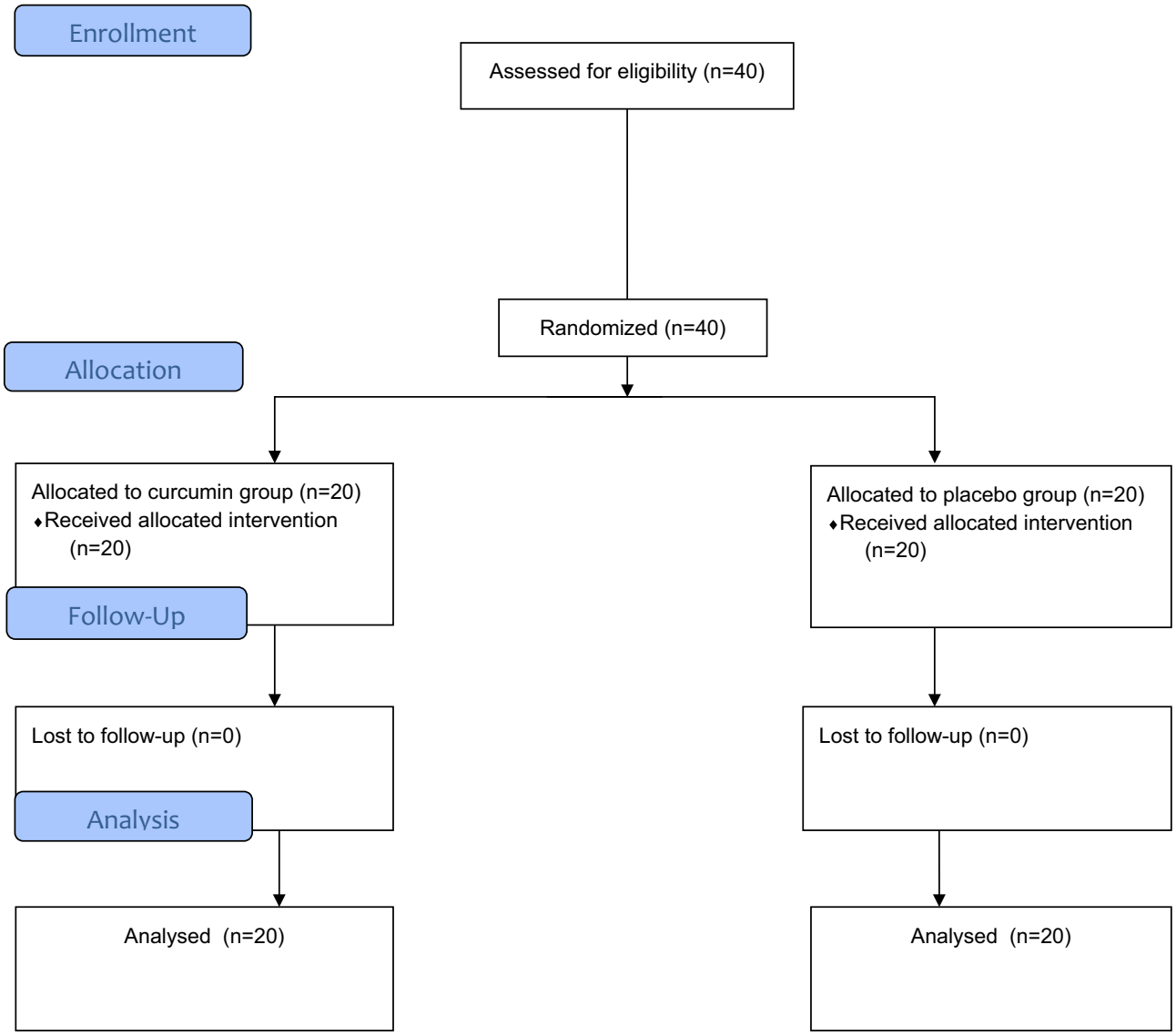

Figure 1. Consort 2010 flow chart.

drugs remained constant during the study. Also, patients in both groups received nephrovit tablets for 12 weeks as before. Each patient received an order number and received the drugs in prepackaged bottles. All drugs and placebo pills were the same color, weight, shape, and size. Patients were followed up every week by two researchers through phone calls to ensure that there were no side effects from receiving the medicine. Clinic researchers, laboratory personnel, data analysts, and patients did not know the treatment process and to which group each patient belonged. Before and after the intervention, auditory brainstem responses (ABR) tests were performed for all subjects. The rationale for selecting this test was comprehensive evaluation of hearing including any retro cochlear pathology. The ABR protocols were delivering 2000 clicks at a rate of 11.1 Hz. The calibration was done after obtaining five ABRs of normal controls for any further comparison. In this test, three electrodes were placed on the patient's forehead, right ear, and left ear, and after clicking the right ear, the waves evoked by the EP25 intra-acoustic (Copenhagen, Denmark) system were recorded with otoaccess software (Middelfart, Denmark)[21]. Then, the hearing threshold level, delay, amplitude, shape, and intervals of waves I, III, and V were evaluated, and data analysis was done in the studied groups. All the hearing tests before and after taking the trial in both groups were done by the same person at the same place with the same machines, and that person (AD) did not know which group each patient belonged to.

Ethical considerations

The study protocol was carried out according to the Declaration of Helsinki. This study was approved by the National Committee for Ethics in Biomedical Research with the ethical code of I.R.SUMS.REC.1400.337, registered in the Iranian Registry of Clinical Trials (irct.ir) (IRCT20210620051629N1), trial registration date was 18/08/2021. All patients completed the consent form before participating in the study.

Statistical analysis

Data was analyzed in the Statistical Package for the Social Sciences (SPSS) version 16 and GraphPad Prism 6 software (GraphPad Software Inc., San Diego, CA, USA). We used Wilcoxon Signed Ranks Test as a non-parametric test of paired t-tests, Mann–Whitney Test as a non-parametric test of student t-test, and chi-square. In all analyses, a $p < 0.05$ was considered statistically significant.

Ethics approval

The protocol was under the Declaration of Helsinki and approved by the National Committee for Ethics in Biomedical Research with the ethical code of IR.SUMS.REC.1400.337. Also, it is registered in the Iranian Registry of Clinical Trials (irct.ir) (IRCT20210620051629N1).

Consent statement

Informed consent was obtained from all the participants.

Results

Our studied population consisted of 40 CKD patients (21 men and 19 women) referred to Shiraz University of Medical Sciences clinics who had impaired hearing function in the initial evaluation. The mean age of participants in the trial (n = 20) and placebo (n = 20) groups were 41.5 ± 7.2 years and 43.2 ± 6.8 years, respectively. Also, the mean glomerular filtration rate (GFR) in the trial group was 42.6 ± 8.8 ml/min/m^2, and in the placebo group was 39.6 ± 9.2 ml/min/m^2 (Table 1).

Curcumin was safe at the dose used and no adverse events or side effects were observed during curcumin treatment in CKD patients and the percentage of adherence to the capsules by participants was 100%.

Auditory function in both groups was studied before and after 12 weeks of treatment. Interval waves III and V in the trial group were 2.7 ± 0.5 ms (ms) and, after treatment, became 2.5 ± 0.5 ms, which showed a significant improvement. Also, interval waves III and V in the placebo group were 2.5 ± 0.4 ms and raised to 2.6 ± 0.5 ms after 12 weeks, which had significant degradation (Table 2, Fig. 2A).

In addition, the latency of wave V in the curcumin group ameliorated significantly after the treatment period (before: 6.2 ± 0.4 ms and after: 5.8 ± 0.4 ms). The latency of wave V in the placebo group was 6.3 ± 0.4 ms and 6.2 ± 0.5 ms, respectively, and did not have a significant change (Table 2, Fig. 2B).

The auditory brainstem response (ABR) threshold in the curcumin group significantly improved after treatment with curcumin and changed from 40.8 ± 11.6 decibel (dB) to 29.8 ± 12.6 dB. ABR threshold in participants in the placebo group did not change significantly and were respectively 32.3 ± 10.1 dB and 33.0 ± 9.7 dB before and after the study (Table 2, Fig. 2C).

None of the 20 participants in the curcumin group had normal hearing before conducting the research; 11 patients had mild hearing loss, seven patients had moderate, and 2 had severe hearing loss. After treatment, nine patients had normal hearing, 9 had mild hearing loss, and none had moderate hearing loss. However, two patients with severe hearing loss have not changed. In the placebo group, in the beginning, none of the patients had normal hearing; 15 had mild hearing loss, 4 had moderate hearing loss, and a patient had severe hearing loss, which changed to no patient with normal hearing, 15 mild, three moderate, and two severe hearing loss after the test (Table 2).

Speech reception threshold (SRT) and speech discrimination score (SDS) were performed on participants before and after the trial. SDS in the curcumin group had a significant increase from (91.3% ± 5.1 to 94.7% ± 4.8) and significantly decreased in the placebo group (from 97.0% ± 4.8 to 96.4% ± 5.8) (Table 2, Fig. 3A). SRT in the trial group went from 37.5 ± 12.1dB to 30.0 ± 12.8 dB and had a significant decrease, and in the placebo group, there were no significant changes (from 30.0 ± 12.7 dB to 29.5 ± 13.2 dB) (Table 2, Fig. 3B).

Characteristics	Studied Groups, N = 40		
	Curcumin (n = 20)	Placebo (n = 20)	*p* Value
Age, (year), Mean ± SD	41.5 ± 7.2	43.2 ± 6.8	NS
Gender, n (%)			
Men	11 (55)	10 (50)	NS
Women	9 (45)	10 (50)	
Body mass index, (kg/m^2), Mean ± S.D	27.8 ± 3.2	25.9 ± 2.6	NS
Marital status, n (%)			
Married	16 (80)	15 (75)	–
Divorced	2 (10)	2 (10)	
Single	2 (10)	3 (15)	
Disease duration, (year), Mean ± SD	3.5 ± 1.5	4.2 ± 2.2	NS
GFR, (ml/min/m^2), Mean ± SD	42.6 ± 8.8	39.6 ± 9.2	NS
Serum creatinine, (mg/dL), Mean ± SD	1.5 ± 0.3	1.4 ± 0.4	NS
Blood urea nitrogen, (mg/dL), Mean ± SD	23.4 ± 10.6	18.2 ± 9.4	NS

Table 1. Baseline characteristics of our studied groups. GFR: Glomerular filtration rate, NS: not significant.

Auditory function, Mean ± S.D	Studied Groups, N = 40		
	Curcumin (n = 20)	Placebo (n = 20)	*p* value
Interval waves III and V (ms)			
Before trial	2.7 ± 0.5	2.5 ± 0.4	NS#
After trial	2.5 ± 0.5	2.6 ± 0.5	
p value*	**< 0.0001**	**0.005**	
Latency of wave's V (ms)			
Before trial	6.2 ± 0.4	6.3 ± 0.4	NS#
After trial	5.8 ± 0.4	6.2 ± 0.5	
p value*	**< 0.0001**	0.283	
ABR threshold (dB)			
Before trial	40.8 ± 11.6	35.3 ± 10.1	NS#
After trial	29.8 ± 12.6	36.0 ± 9.7	
p value*	**< 0.0001**	0.083	
ABR threshold group, n (%)			
Before trial			
Normal hearing	0 (0.0)	0 (0.0)	NS+
Mild hearing loss	11 (55.0)	15 (75.0)	
Moderate hearing loss	7 (35.0)	4 (20.0)	
Severe hearing loss	2 (10.0)	1 (5.0)	
After trial			
Normal hearing	9 (45.0)	0 (0.0)	**0.044+**
Mild hearing loss	9 (45.0)	15 (75.0)	
Moderate hearing loss	0 (0.0)	3 (15.0)	
Severe hearing loss	2 (10.0)	2 (10.0)	
SDS (%)			
Before trial	91.3 ± 5.1	97.0 ± 4.8	NS#
After trial	94.7 ± 4.8	96.4 ± 5.8	
p value*	**0.001**	**0.014**	
SRT (dB)			
Before trial	37.5 ± 12.1	30.0 ± 12.7	NS#
After trial	30.0 ± 12.8	29.5 ± 13.2	
p value*	**< 0.0001**	0.157	

Table 2. Comparison of the ABR and PTA test among the studied groups. *: Wilcoxon Signed Ranks Test. +: Chi-square Test. #: Mann–Whitney Test. ABR threshold: Auditory brain stem response threshold, SDS: Speech discrimination score, SRT: Speech reception threshold, NS: not significant. Significant values are in bold.

Discussion

Our study showed that after 12 weeks of curcumin treatment, CKD patients' auditory function significantly improved. ABR threshold, III–V waves interval, Latency of wave V, SDS, and SRT were improved significantly after curcumin treatment compared to controls. The rate of hearing improvement after curcumin treatment in our study was 55% (Table 2). Our findings suggest a potential beneficial effect of curcumin on hearing loss in CKD patients, which warrants further investigation.

As previously mentioned, due to the similar antigenicity and physiological mechanisms between the renal nephron and the labyrinth, a reduction in renal function can independently be associated with hearing loss[7]. Previous studies have shown that in most cases, CKD patients suffer from chronic inflammation, and the progression of chronic renal failure can lead to inflammation and oxidative stress[22,23].

Experimental research has shown that an antioxidant compound such as rutin improved hearing damage caused by diabetes mellitus[24], but folic acid did not affect the hearing system[25].

With broad biological functions, curcumin can target several signaling pathways and has antioxidative and anti-inflammatory properties. Curcumin can directly react with radical species and increase the gene expression of proteins with cytoprotective and antioxidant activities. Downregulation of profibrotic cytokines, TGF-β, vascular endothelial growth factor (VEGF), osteopontin, and connective tissue growth factor (CTGF), and effects of extracellular matrix proteins such as fibronectin and collagen IV are among the factors that cause the protective effect of curcumin against kidney damages[26,27]. So far, no study has been conducted on the impact of curcumin on hearing loss in chronic kidney failure patients. A survey by Bucak et al. on 40 Sprague–Dawley rats showed that curcumin could significantly protect cochlear morphology and functions from paclitaxel-induced toxicity[28].

Li et al. investigated the effect of curcumin on age-related hearing loss in an animal model study, and it showed that curcumin could reduce cell senescence and apoptosis caused by H_2O_2 in auditory hair cells and prevent

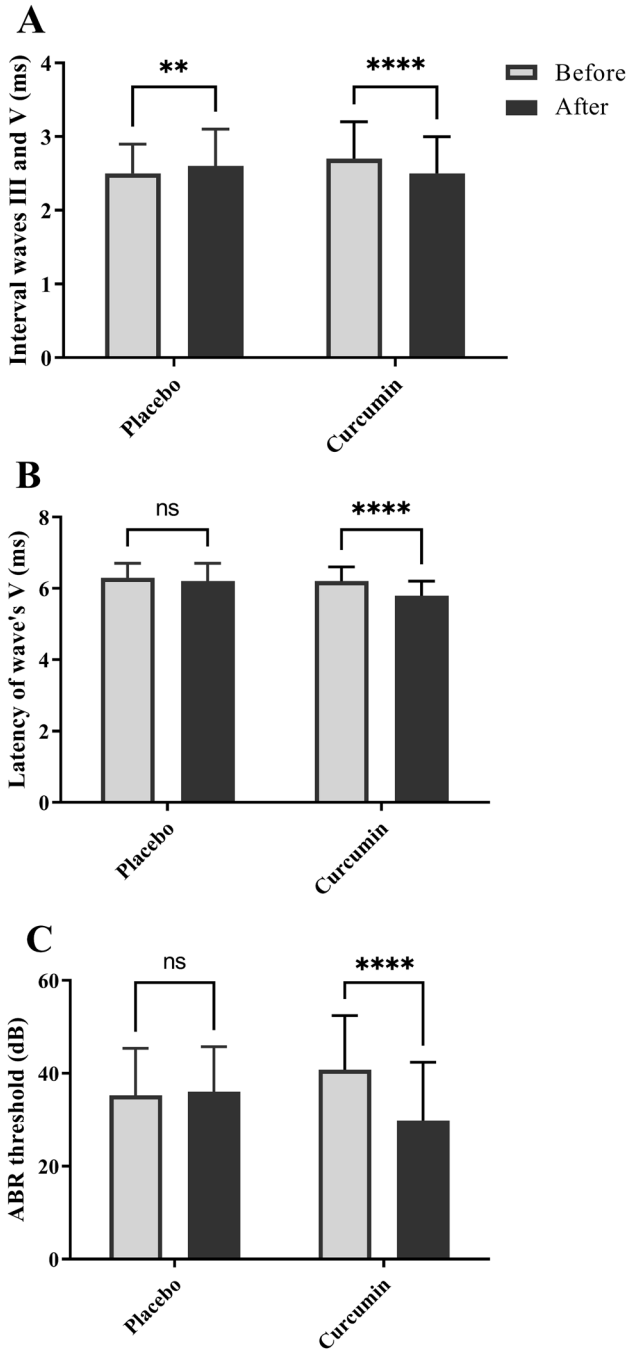

Figure 2. (**A**) Interval waves III and V, (**B**) Latency of wave's V, (**C**) ABR threshold in placebo and Curcumin group before and after treatment. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, and ****: $p < 0.0001$ represents statistically significant between groups.

mitochondrial dysfunction. Curcumin can prevent the degeneration of auditory hair cells caused by oxidative stress by activating and elevating the expression of Nrf2[19]. Furthermore, curcumin attenuates the expression of calcineurin, NFATc1, and the apoptosis index of cochlear fibroblasts, leading to its potential effectiveness in the prevention and treatment of fibroblast damage in cochlear supporting tissues and lateral wall[29].

Polyphenols such as curcumin and ferulic acid are agents that modify oxidative stress and inflammation; in a study by Paciello et al., both Curcumin and ferulic acid by up-regulating Nrf-2/HO-1 pathway and downregulating p53 phosphorylation showed antioxidant and hearing protective activity in the cochlea thus protecting against cisplatin-induced ototoxicity. In addition, only curcumin can affect inflammatory pathways that counteract NF-κB activation[30].

Castañeda et al. investigated the effect of traditional medicine agents, including curcumin, in reducing sensorineural hearing loss. The result indicated that conventional medicine drugs improve microcirculation in the

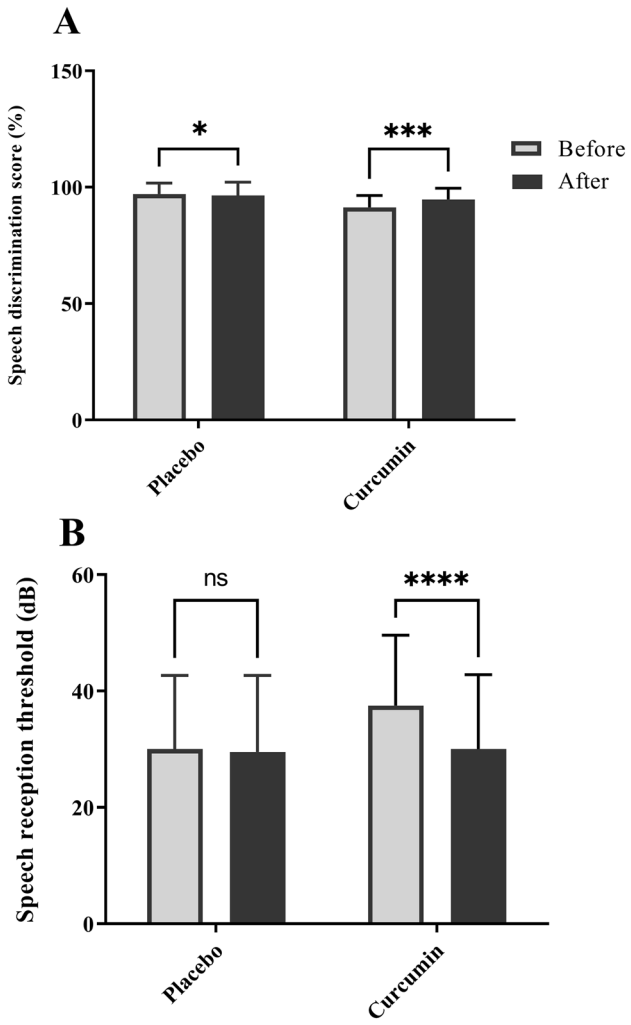

Figure 3. (**A**) Speech discrimination score, (**B**) Speech reception threshold in placebo, and Curcumin group before and after treatment. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, and ****: $p < 0.0001$ represents statistically significant between groups.

blood-labyrinth barrier. Also, antioxidative, anti-inflammatory, antiapoptotic properties, and neuroprotective activities are some of their potential benefits[31].

Doluperine capsules, which consist of curcumin, piperine, and gingerol, showed a positive effect on hearing recovery of sudden sensorineural hearing loss in diabetic patients, along with steroid therapy[32].

Curcumin protects auditory hair cells by reducing damage caused by oxidative stress. It also helps prevent cell death and the aging of cells, ultimately supporting the health and function of auditory hair cells. The way curcumin protects cells is primarily by activating a certain pathway called Nrf2/HO-1[19].

The problem concerning curcumin is its low bioavailability due to poor intestinal absorption, rapid metabolism, binding to hydrophilic molecules in the liver with biliary excretion, poor water solubility, and body clearance. Animal and human studies have demonstrated that significant pharmacological effects require high doses of curcumin, although studies have also shown that curcumin is safe even at high doses[33–36]. The bioavailability of curcumin can be increased by nanotechnology methods such as liposomal curcumin, curcumin phospholipid complex, curcumin nanoparticles, and curcumin structural analogs[37].

Finally, improving hearing performance in patients with CKD can enhance their quality of life and result in reduced healthcare resource utilization.

Conclusion

According to the results of the auditory function tests in this study, there is a statistically significant difference between patients receiving curcumin and those receiving placebo, and after twelve weeks, receiving 500 mg of curcumin daily significantly improved hearing loss in CKD patients. Therefore, using curcumin as a therapeutic agent for treating hearing loss in patients with chronic kidney disease can be an option. However, more extensive studies on the effects and side effects with a larger sample size are recommended.

Data availability

All include both original data generated in our research and any secondary data reuse that supports our results and analyses data is presented within the manuscript file.

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Author contributions
A.D., K.I., L.M. and J.R. contributed to the design, drafted the manuscript, analyzed data, approved the final version, and accepted accountability for the overall work. G.G. and A.S. contributed to data collection, revised the manuscript, approved the final version, and accepted responsibility for the general result.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to J.R.

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