INTRODUCTION

Inner ear impairment can be characterised by cochlear dysfunction or vestibular dysfunction or both. Sensorineural hearing loss (SNHL) has a high prevalence and can cause significant adverse impact on an affected individual’s quality of life. The pathophysiological mechanisms involved in SNHL include vascular ischaemia, oxidative stress and inflammation.

Hyperlipidaemia has been reported to be associated with sudden sensorineural hearing loss (SSNHL) and noise-induced hearing loss (NIHL). One possible explanation regarding the mechanism of hearing damage by dyslipidaemia involves vascular ischaemia of the inner ear artery. Hyperlipidaemia increases plasma viscosity which can trigger the stenosis of the cochlear artery leading to cochlear ischaemia and subsequent SNHL; therefore, vascular compromise is regarded as playing a vital role in SNHL.

Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, commonly known as statins, are widely used as cholesterol-lowering drugs. Due to the strong evidence supporting cardiovascular benefits of its usage, statin therapy to reduce high cholesterol is recommended for people with cardiovascular risk factors. The overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond cholesterol reduction such as improved endothelial function and microcirculation, reduced oxidative stress and decreased inflammation.

The efficacy of statins as otoprotective agents: A systematic review

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Abstract

Objective: This systematic review examined the current literature, summarised research findings and identified research gaps regarding the efficacy of statins on audiological outcomes.

Methods: Systematic search of electronic databases and grey literature was performed. Eligibility criteria were the study of a statin drug with report of audiological outcomes such as hearing, tinnitus or balance in either human or animal studies. Data extraction and quality assessment were performed by two independently researchers. The characteristics of the study and research findings were collated and summarised. A narrative synthesis was conducted. Meta-analysis was not possible due to heterogeneity of the included studies.

Results: Analysis of searches yielded 17 studies meeting the criteria. Included studies had variable drug type and dosage, outcome measures and associated inner ear conditions. Most animal experiments showed promising audiological outcomes after statin treatment, demonstrated by the results of auditory brainstem response, distortion product otoacoustic emissions and inner ear histology. However, no clear effect can be discerned in human trials due to the mixed results, and heterogeneity in research methodology and quality. Audiological outcomes were not always correlated with cholesterol levels.

Conclusions: Statins remain a potential candidate as otoprotective agents which warrant further investigation.
The effect of statins, including the cholesterol lowering, antioxidative and anti-inflammatory properties, could be beneficial as an otoprotective agent involving both haemodynamic and metabolic mechanisms. This is of interest because hearing loss associated with hyperlipidaemia would be thereby potentially treatable. There has so far been little evidence to support their use in the treatment or prevention of inner ear dysfunction; hence, statins are not routinely used for this purpose. This systematic review examined current literature on the efficacy of statins on audiological outcomes.

2 | METHOD

2.1 | Identify relevant studies

The following databases were searched: Medline, EMBASE, IPA (International Pharmaceutical Abstracts) and ClinicalTrials.gov. Grey literature was also sought through the conference abstracts searching on Google Scholar. The steps followed the PRISMA guideline. Standardised terms and keywords were merged in the search for concepts of statin drugs and otoprotection. Study details were registered on PROSPERO (CRD42019133701). The search was limited to the English language because of resource constraints. The search strategies are reported in Appendix 1.

2.2 | Study selection

Eligibility criteria for records to be included were the study of a statin with reporting of audiological outcomes such as hearing, tinnitus or balance in either human or animal studies. All study types were eligible except review articles and in vitro studies. Two screening steps were undertaken independently by two authors. The first step checked that each title and abstract was within the scope of research question. The second step considered the eligibility criteria. Discrepancies were resolved through discussion.

2.3 | Data extraction

Data from each included study were extracted independently by two clinical experts on the team (PP, an otorhinolaryngologist and DB, an audiologist) using a data extraction form. Pre-specified data items included study design, participant demographics, sample size, drug type and dosage, and outcome evaluation. Discrepancies were identified and resolved through discussion.

2.4 | Quality assessment

The reviewers independently assessed the methodological quality of the articles by applying the National Institutes of Health (NIH) Quality Assessment Tool. If the ratings were different, then reviewers discussed the article in an effort to reach consensus. The score was assigned for each item: “Yes” was scored 1, and “No” or “Cannot determine” or “Nor reported” was scored 0. The summary score of each study was calculated, expressed as a percentage and could range from 0% to 100%. These were categorised into four categories: poor (0%-25%), fair (26%-50%), good (51%-75%) or excellent (76%-100%). The quality score was not used as the criteria for eligibility because of the limited literature on this topic.

2.5 | Data synthesis

A narrative synthesis was implemented for the present systematic review, as there were high heterogeneities of studies included. The characteristics of the study and research findings were collated and summarised.

3 | RESULTS

A summary of the study selection processes with the reasons for exclusion is represented in Figure 1. Seventeen individual studies were included for data extraction. The results are presented in a narrative summary and review. We did not perform a meta-analysis as the studies were heterogeneous, and several of them were observational designs.

3.1 | Descriptions of included studies

Nine articles revealed human studies comprising of one RCT, three pre–post–studies, two cohort studies, two retrospective studies and two case reports. Eight animal studies included two randomised studies and six non-randomised controlled interventional studies.20-27

3.2 | Quality assessment

The mean score on the NIH Quality Assessment Tool was 38% (range 7%-79%). There were eight studies (47%) with fair quality; five studies (29%) with poor quality; three studies (18%) with good quality; and one study (6%) with excellent quality (See Table 1).

Key points

- Animal experiments presented promising audiological outcomes, demonstrated by electrophysiological results and inner ear histology.
- Human trials showed no clear effect due to the mixed results, and heterogeneity in research methodology and quality.
- Audiological outcomes were not always correlated with cholesterol levels.
- Statins remain a potential candidate as otoprotective agents which warrant further study.
3.3 | Human studies

Outcome measurements were highly variable among studies and included audiometry,\textsuperscript{11,13,15,17-19} tinnitus questionnaire,\textsuperscript{11,17} Tinnitus Handicap Questionnaire (THQ),\textsuperscript{14} tinnitus degree/severity/loudness,\textsuperscript{13} self-reports of tinnitus\textsuperscript{19} and vertigo symptoms.\textsuperscript{16} The summary of characteristics and results of included human studies are demonstrated in Table 1.

Two studies classified participants into responsive and unresponsive groups according to cholesterol levels after the treatment and then compared the audiological outcomes.\textsuperscript{12,14} The criteria for responsive and non-responsive individuals were substantially different. Cholesterol responsive was defined by a return to normal cholesterol or triglyceride level but normal levels were not specified,\textsuperscript{13} or cholesterol level less than 200 mg/dL.\textsuperscript{14}

3.3.1 | Audiometry

Mixed results were reported with two studies concluding no improvement in hearing threshold,\textsuperscript{11,17} and four studies reporting some improvement.\textsuperscript{12,13,18,19} Two studies reported a correlation between statin use and a reduced prevalence of hearing loss.\textsuperscript{15,18}

There was no significant difference in pure-tone thresholds between atorvastatin and placebo groups.\textsuperscript{11} Another study reported no significant difference in hearing threshold between simvastatin and ginkgo groups.\textsuperscript{17}

Nine out of twelve (75%) patients with chronic-phase SSNHL had hearing improvement in at least two frequencies.\textsuperscript{12} There was a significant improvement of hearing threshold at higher frequencies in the cholesterol treatment responsive group compared with the unresponsive group.\textsuperscript{13} Improvement in THQ score by at least 10 points was seen in 70.5% of patients in cholesterol responsive group compared with 4.2% in cholesterol unresponsive group.\textsuperscript{14} A case report described a substantial hearing improvement after rosuvastatin therapy.\textsuperscript{19}

3.3.2 | Tinnitus

Studies described varied results of no significant improvement of tinnitus\textsuperscript{11,17} and significant improvement.\textsuperscript{13,14,19}

There was a trend towards relief of tinnitus in the atorvastatin group while tinnitus severity scores were rather stable in the placebo group.\textsuperscript{11} In another study, there was no significant difference in tinnitus score between simvastatin and ginkgo groups.\textsuperscript{17}

There was a significant improvement of tinnitus intensity and self-rated tinnitus in cholesterol responsive group relative to cholesterol non-responsive group.\textsuperscript{13} Improvement in THQ score by at least 10 points was seen in 70.5% of patients in cholesterol responsive group compared with 4.2% in cholesterol unresponsive group.\textsuperscript{14} A case report described complete relief of tinnitus after statin therapy.\textsuperscript{19}

3.3.3 | Vertigo

One article reported that 84% of vertiginous patients had complete resolution of vertigo, and total remission in one case of recurrent vertigo after statin treatment.\textsuperscript{16}

3.3.4 | Cholesterol level and audiological outcomes

Most patients who received statin treatment had elevated cholesterol levels ranging from 100-190\textsuperscript{11} to 239-356\textsuperscript{14} mg/dL. However, specified criteria of hyperlipidaemia or cholesterol levels were not reported in some studies.\textsuperscript{13,15,16,18}

![FIGURE 1 Flow chart of stages of the study selection process](image-url)
| Study no. | Title                                                                 | Sample size | Study population                      | Statin drug, dosage and duration | Outcome measures                  | Audiological outcomes                                      | Cholesterol levels | NIH score (%) |
|----------|------------------------------------------------------------------------|-------------|----------------------------------------|----------------------------------|-----------------------------------|-------------------------------------------------------------|--------------------|--------------|
| 1        | Effect of atorvastatin on progression of sensorineural hearing loss and tinnitus in the elderly; results of a prospective, randomised, double-blind clinical trial⁴¹ | 48          | Adults with presbycusis                | Atorvastatin 40 mg OD            | • Audiometry                      | Mean deterioration of hearing threshold of all ears in all frequencies was 1.30 dB in the atorvastatin and 1.07 dB in the placebo group. There was no significant difference between both groups. • Trend towards a reduction of tinnitus score but not significant. Atorvastatin group: 38.3 -> 34.8 -> 27.6 Placebo group: 23.6 -> 24.8 -> 26.8 | LDL-c level was 100-190 mg/dL before treatment. • Significant reduction of total cholesterol and LDL-c in atorvastatin group (Levels not reported). | 72            |
| 2        | Hearing improvement after therapy for hyperlipidaemia in patients with chronic-phase sudden deafness⁴² | 12          | Adults with unilateral SSNHL           | Pravastatin for 90-519 days      | • Audiometry                      | Nine patients had hearing improvement (>10 dB) in more than 1 frequency • Mean hearing level had improved significantly at 125, 250, 500 and 2000 Hz. | Mean cholesterol level was 247.2 mg/dL before treatment, and decreased to 202.8 mg/dL after treatment. | 58            |
| 3        | Low-cholesterol diet and antilipid therapy in managing tinnitus and hearing loss in patients with noise-induced hearing loss and hyperlipidemia | 42          | Adults with subjective tinnitus and hearing loss due to noise exposure | Simvastatin 10-40 mg OD or Atorvastatin 10-80 mg OD for 1-2 year | • Audiometry • Tinnitus degree • Tinnitus severity • Tinnitus loudness | Comparing cholesterol responsive (N = 20) and unresponsive (N = 22) groups • Significant improvement of hearing threshold at 4000 and 8000 Hz but no significant difference at 500, 1000, and 2000 Hz in responsive group. • Significant improvement of tinnitus degree and severity in responsive group. | Cholesterol responsive was defined by a return to normal cholesterol or triglyceride level (normal levels were not specified). • Cholesterol level before treatment was not reported. | 42            |
| 4        | Atorvastatin in the management of tinnitus with hyperlipidaemias⁴⁴    | 98          | Adults with tinnitus and SNHL at least 1 year | Atorvastatin 40 mg OD for 8 weeks | • THQ | Comparing cholesterol responsive (N = 51) and unresponsive (N = 47) groups • Improvement in tinnitus score in the responsive group was seen in 36 (70.5%) patients and in 2 (4.2%) patients of the unresponsive group. | Cholesterol responsive was defined by cholesterol level less than 200 mg/dL. • Cholesterol level before treatment was 239-356 mg/dL. | 33            |
| 5        | Dietary intake of cholesterol is positively associated and use of cholesterol-lowering medication is negatively associated with prevalent age-related hearing loss⁴⁵ | 274         | Adults with presbycusis                | Statins                          | • Audiometry                      | Reduced odds of having impaired hearing among those reporting statin use in both cross-sectionally and longitudinally. • Persons self-reporting statin use were 48% less likely to have hearing loss after multi-variable adjustment [OR = 0.52; 0.29-0.93]. | NR                | 79           |
| 6        | Vestibular vertigo associated with hyperlipidaemia: response to antilipidaemic therapy⁴⁶ | 31          | Adults with recurrent vertigo          | Lovastatin or Pravastatin 20-40 mg/d | • Vertigo symptoms                | 84% of patients in a cohort had complete resolution of vertigo. • Total remission of vertigo and did not recur in a case report. | NR                | 7            |

(Continues)
| Study no. | Title                                                                 | Sample size | Study population | Statin drug, dosage and duration | Outcome measures                  | Audiological outcomes                                           | Cholesterol levels                                                                 | NIH score (%) |
|----------|----------------------------------------------------------------------|-------------|------------------|----------------------------------|-----------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------|--------------|
| 7        | Simvastatin and Ginkgo biloba in the treatment of subacute tinnitus: a retrospective study of 94 patient⁷⁷ | 94          | Adults with moderate to severe tinnitus | Simvastatin 40 mg OD for 4 months | • Audiometry • Tinnitus questionnaire | • There was no significant difference in hearing thresholds between simvastatin and ginkgo groups • There was no significant improvement in tinnitus scores between both groups. Simvastatin group: 41.4 -> 37.3 Ginkgo group: 44.7 -> 41 | • Mean cholesterol level was 243 mg/dL before statin treatment and reduced to 195 mg/dL after treatment. • Mean cholesterol level was 239 mg/dL in ginkgo group. | 43           |
| 8        | Concurrent use of cholesterol-lowering drugs may reduce the incidence of ototoxicity in cisplatin-treated patients⁸⁸ | NR          | Adults received cisplatin chemotherapy | Lovastatin                       | • Audiometry                      | • A reduced incidence and severity of cisplatin-induced hearing loss in statin users relative to individuals who were not on a concurrent statin therapy. | NR                                                        | 21           |
| 9        | Hearing loss due to familial hypercholesterolaemia and statin treatment⁹⁹ | 1           | An adult with SSNHL, tinnitus and positional vertigo | Rosuvastatin 40 mg OD for 1 year | • Audiometry • Tinnitus status | • There was a substantial improvement of hearing test and complete regression of tinnitus. | • Total cholesterol level was 316 mg/dL and LDL-c level was 234 mg/dL before treatment. • LDL-c level was 110 mg/dL, 1 y after treatment. | 15           |

Abbreviations: LDL-c, low-density lipoprotein cholesterol; NR, not reported; OD, once daily; THQ, Tinnitus Handicap Questionnaire; SSNHL, sudden sensorineural hearing loss.
Successful cholesterol lowering was associated with significant improvement of tinnitus\textsuperscript{13,14} and hearing threshold.\textsuperscript{13} Another two studies also showed parallel results of cholesterol lowering and hearing improvement.\textsuperscript{12,15} On the other hand, two studies reported no audiological improvement despite cholesterol reduction after statin treatment.\textsuperscript{11,17}

3.4 | Animal experiments

Outcome measurements were highly variable among studies and include auditory brainstem response (ABR),\textsuperscript{20,22,24,27} distortion product otoacoustic emissions (DPOAE),\textsuperscript{21,23,24} and inner ear histology.\textsuperscript{20,22,25} The summary of characteristics and results of included animal studies are reported in Table 2.

3.4.1 | ABR

Most of the included studies reported protection of hearing detected by ABR,\textsuperscript{20,22,24,27} except in one study.\textsuperscript{21} Cai et al.\textsuperscript{20} found that hearing thresholds remained stable at 40 dB in simvastatin-treated mice fed with high-lipid diet while significant increased hearing thresholds from 35 dB to 60 dB were observed in the non–statin-treated group. Three studies demonstrated the efficacy of statins to prevent NIHL.\textsuperscript{22,26,27} Park et al.\textsuperscript{22} revealed a significantly decreased hearing threshold shift of approximately 20 dB in the pravastatin-pre-treated group of mice compared with the noise-only group at 1 and 14 days. ABR threshold after noise exposure was 5.83 dB in fluvastatin-treated mice, which was substantially lower than the 41.7 dB in the noise-only group.\textsuperscript{27} Another study reported that fluvastatin given 7 days before noise exposure can protect the inner ear against NIHL in the guinea pigs.\textsuperscript{26} Statin treatment prior to acoustic injury appeared to be more effective than when given after noise exposure.\textsuperscript{26} Only one study examined statin treatment in cisplatin ototoxicity, reporting that ABR thresholds were significantly protected in cisplatin-treated mice receiving prior lovastatin relative to cisplatin-only treated mice.\textsuperscript{24} Furthermore, hearing preservation was observed in diabetic mice treated with atorvastatin but without detailed information.\textsuperscript{25}

In contrast, there were no significant differences in hearing thresholds between atorvastatin-treated mice and control mice, but all animals had normal hearing threshold.\textsuperscript{21}

3.4.2 | DPOAE

Three studies reported DPOAE results: all showed positive auditory outcomes of statin usage.\textsuperscript{21,23,24} Two of three studies reported both ABR and DPOAE outcomes.\textsuperscript{21,24} The results were concordant in one study which demonstrated the preservation of both ABR threshold and DPOAE in the lovastatin-treated group.\textsuperscript{24} Conversely, another study demonstrated better results of DPOAE in atorvastatin-treated mice though no significant differences in hearing thresholds detected by ABR.\textsuperscript{21}

3.4.3 | Inner ear histology

Three studies reported histological findings of the inner ear in animals.\textsuperscript{20,22,25} After statin administration, there was preservation of the numbers and morphology of hair cells and spiral ganglia in hyperlipidaemic mice,\textsuperscript{20} and spiral ganglia and stria vascularis in diabetic mice.\textsuperscript{27} Conservation of hair cells was also demonstrated after noise exposure.\textsuperscript{22}

3.4.4 | Cholesterol level and audiological outcomes

Hearing improvements corresponded to the results of cholesterol lowering in two studies,\textsuperscript{20,22} but not related to cholesterol level in one study reported.\textsuperscript{21} Nonetheless, cholesterol levels were not reported in five studies.\textsuperscript{23,27}

Normal hearing findings, alongside lower cholesterol levels and much less severe atherosclerotic lesions in simvastatin-treated mice, support the role statin drugs play in the protection of hearing loss.\textsuperscript{20} Interestingly, the inner ear protection efficacy of statins was also found when cholesterol-lowering effects were absent.\textsuperscript{21}

4 | DISCUSSION

Current literature regarding a potential otoprotective effect of statin drugs has high variability in drug type and dosage, outcome measures and associated inner ear status. Most of the studies were classified to have fair or poor quality, and a significant portion of included studies retrieved from grey literature reported limited information. Most animal experiments showed promising audiological results; however, no clear effect can be discerned from human trials. The differences between animal experiments and human studies are potentially due to the difference in species, equivalent drug dosage and outcome measurements.

4.1 | Drug type, dosage and timing of administration

Statin type and dosage varied among studies. While low-dose atorvastatin used before exposure to noise can potentially prevent NIHL in rats, the effect was not observed in higher doses.\textsuperscript{23} Animal studies demonstrated a protective effect when the drug was administered before or during noise exposure but showed limited efficacy when given after noise exposure.\textsuperscript{22,23,26,27} This could be explained by the pathophysiology of ROS production in that ROS is hard to overcome when it has occurred but prevention by diminishing the inflammatory process is more effective.

4.2 | Outcome measures

Most of the animal experiments demonstrated favourable outcomes of ABR and DPOAE in statin-treated animals, supported by histological findings. The discrepancy between ABR and DPOAE results in
| Study no. | Title                                                                 | Sample size | Study animals | Statin drug, dosage and duration | Outcome measures                  | Audiological outcomes                                                                 | Cholesterol levels                          | NIH score (%) |
|----------|------------------------------------------------------------------------|-------------|----------------|----------------------------------|------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------|----------------|
| 1        | Effects of simvastatin on plasma lipoproteins and hearing loss in apolipoprotein E gene-deficient mice | 30          | Mice           | Simvastatin oral for 14 weeks     | ABR at 0.3-3 kHz                   | Hearing thresholds remained stable at 40 dB in simvastatin-treated group and significant increased hearing thresholds from 35 dB to 60 dB in no statin-treated group. | Total cholesterol levels were 131 mg/dL in simvastatin-treated group, and 253 mg/mL in non-treated group. | 36             |
|          |                                                                        |             |                |                                  | Histology                          | Preservation of hair cells and neurons in the spiral ganglion in simvastatin-treated group. | LDL-c levels were 133 mg/dL in simvastatin-treated group, and 198 mg/dL in non-treated group. |                |
| 2        | Atorvastatin slows down the deterioration of inner ear function with age in mice | 50          | Mice           | Atorvastatin oral 10 mg/kg/d for 8 weeks | ABR at 0.3-10 kHz DPOAE at 4-40 kHz | All animals had normal hearing thresholds. No significant differences in hearing thresholds between atorvastatin-treated group and control group. Larger amplitudes of DPOAE in atorvastatin-treated wild type mice especially at high frequencies (19-27 kHz). | Atorvastatin treatment did not affect cholesterol levels in wild type mice. | 57             |
| 3        | Pravastatin attenuates noise-induced cochlear injury in mice           | 29          | Mice           | Pravastatin oral 25 mg/kg/d for 5 days prior to noise exposure and/or 3 days after noise exposure | ABR at 16 and 32 kHz Histology     | Hearing thresholds were 43.2-47.4 dB in the noise-only group, and 23.8-27.4 dB in the pravastatin-pre-treated group at 1 day after noise exposure. Hearing thresholds were 41.9-45.9 dB the noise-only group, and 21.5-23.8 dB in the pravastatin-pre-treated group at 14 days after noise exposure. No increased attenuation of threshold shift when pravastatin was further administered after noise exposure, compared with the pre-exposure group. Increase hair cells survival rate in statin-treated group. | Cholesterol levels in pravastatin group were lower compared with the control group, although cholesterol levels in both groups were within the reference range. | 43             |
| 4        | The effect of atorvastatin on preventing noise-induced hearing loss: an experimental study | 40          | Rats           | Pre-treatment atorvastatin oral 5, 25, and 50 mg/kg/d for 14 days | DPAOE at 2-8 kHz                   | Response amplitude was significantly decreased at all frequencies immediately after exposure to noise in all studied groups. The amplitude increased after 72 hours to a level higher than temporary threshold shift (TTS); this change was only significant in the group received 5 mg/kg atorvastatin. | NR | 29             |

(Continues)
### TABLE 2 (Continued)

| Study no. | Title                                                                 | Sample size | Study animals | Statin drug, dosage and duration                                      | Outcome measures                                                                 | Audiological outcomes                                                                 | Cholesterol levels | NIH score (%) |
|-----------|-----------------------------------------------------------------------|-------------|----------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------|---------------|
| 5         | Protective effects of concurrent statin use against ototoxicity in cisplatin-treated mice | NR          | Mice           | Lovastatin oral 40 or 60 mg/kg/d prior to cisplatin for 2 weeks        | • ABR at 8-40 kHz                                                               | • ABR response thresholds in the low to mid frequencies were significantly protected.      | NR                 | 14            |
|           |                                                                       |             |                |                                                                       | • DPOAE at 8-40 kHz                                                             | • DPOAE were preserved, though reduced.                                                |                    |               |
| 6         | The effect of atorvastatin on hearing impairment in diabetic mice     | 40          | Mice           | Atorvastatin 20 mg/kg IP every other day for 4 weeks                  | • ABR at 16 and 32 kHz                                                          | • There was a preservation of hearing.                                                | NR                 | 43            |
|           |                                                                       |             |                |                                                                       | • Histology                                                                     | • There was a preservation of spiral ganglion neurons and stria vascularis.          |                    |               |
| 7         | Fluvastatin attenuates acoustic injury                                | NR          | Guinea pigs    | Fluvastatin 50 mmol/L direct to left cochlea either 7 days before or after noise exposure | • ABR                                                                            | • Fluvastatin given 7 days before can protect against NIHL.                           | NR                 | 36            |
|           |                                                                       |             |                |                                                                       |                                                                                 | • Fluvastatin given 7 days after noise exposure was not as effective, but did show a mild protection. |                    |               |
| 8         | Fluvastatin protects against high decibel noise-induced hearing loss  | 24          | Guinea pigs    | Fluvastatin direct to left cochlea at the same time as noise exposure | • ABR                                                                            | • ABR threshold elevation after exposure was [41.7 ± 12 dB in noise-only group, and 5.83 ± 10.7 dB for noise-exposed fluvastatin-treated group. | NR                 | 21            |

Abbreviations: ABR, auditory brainstem response; DPOAE, distortion product otoacoustic emission; IP, intraperitoneal; NR, not reported.
Syka et al.\textsuperscript{21} can be explained by the different pathways and sensitivities of the tests.\textsuperscript{28,29}

Tinnitus evaluation varied highly among studies using self-reported symptoms and standard questionnaires which emphasises the difficulty of comparison between studies.

### 4.3 | Inner ear conditions

Tentative evidence identified to support an otoprotective effect of statin against NIHL caused by acoustic overstimulation\textsuperscript{13,22,23,26,27} and cisplatin ototoxicity.\textsuperscript{24} Interestingly, one accepted mechanism shared by these conditions is related to overproduction of ROS,\textsuperscript{30} supporting the proposal of an antioxidative effect of statin treatment. Statin treatment in patients with other SNHL and tinnitus showed mixed results with no benefits\textsuperscript{11,17,21} and some benefits.\textsuperscript{12-15,20,25} Despite these mixed results of statin treatment, some reversibility of hearing loss and tinnitus was demonstrated in the chronic phase.\textsuperscript{12-14,19}

### 4.4 | Cholesterol level and audiological outcomes

Six studies showed positive audiological outcomes accompanied by lower cholesterol levels,\textsuperscript{12-14,19,20,22} indicating cholesterol dependent effects of statin on audiological outcomes. These studies support the pathophysiology of vascular ischaemia associated with hypercholesterolaemia which leads to oxygen reduction, overproduction of ROS and an inflammatory process causing eventually to apoptotic cell death.

In contrast, three studies reported no correlation of inner ear functions and cholesterol-lowering outcomes after statin treatment,\textsuperscript{11,17,21} signifying that hearing outcome may not be associated with cholesterol levels. Syka et al.\textsuperscript{21} showed some efficacy of inner ear protection after statin treatment with no effects on cholesterol levels, supporting the pleiotropic (cholesterol-independent) effects of statins.\textsuperscript{9}

No significant improvement of hearing thresholds and tinnitus were reported in two studies although they showed the successful cholesterol-lowering effect of statins.\textsuperscript{11,17} Olzowy et al.\textsuperscript{11} included only patients who had presbycusis with moderately elevated cholesterol levels and Canis et al.\textsuperscript{17} showed a relatively small change of cholesterol level. It is possible that patients with higher baseline cholesterol levels or who had a larger change of cholesterol level might have a pronounced benefit from statin treatment on cochlear functions.

### 4.5 | Limitations of the study

Some limitations of the current review are that a significant portion of included studies reported limited information, and only publications in the English language were included; thus, language bias may have occurred.

### 5 | CONCLUSION

Included studies had variable methodology and quality. Most animal experiments showed promising results; however, no clear effect was discerned from the results in human trials. Developing therapeutic strategies for the prevention of hearing loss using otoprotective drugs is one of the major goals of current auditory research, and statins remain of interest in this regard.

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**CONFLICTS OF INTEREST**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**DATA AVAILABILITY STATEMENT**

The datasets analysed in this manuscript are not publicly available. Requests to access the datasets should be directed to the corresponding author.

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APPENDIX 1

SEARCH STRATEGY

MEDLINE

1. Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR Anticholesteremic Agents/ OR Hypercholesterolemia/ OR Hyperlipidemia/ OR simvastatin/ OR Atorvastatin Calcium/ OR Rosuvastatin Calcium/ OR Pravastatin/ OR Lovastatin/ OR (Hydroxymethylglutaryl-CoA Reductase Inhibitor* OR Anticholesteremic agent* OR Hypolipidemic agent* OR Cholesterol lowering agent* OR Antilipid agent* OR Antilipemic agent* OR Antilipidemic agent* OR Hypolipidemic agent* OR Lipid lowering agent* OR Statin OR Simvastatin OR Atorvastatin OR Rosuvastatin OR Pravastatin OR Lovastatin OR Fluvastatin OR Pitavastatin),ti,ab.
2. Hearing/OR HearingLoss/OR Tinnitus/OR Dizziness/OR Vertigo/OR Ataxia/OR Ear, inner/or Cochlea/OR Vestibule, labyrinth/OR Hearing test/OR Audiometry/OR Otoacoustic Emissions/OR Evoked Potentials, Auditory/OR Evoked Potentials, Auditory, Brain Stem/OR Caloric Tests/OR Electronystagmography/OR Reflex, Vestibulo-Ocular/OR Vestibular Function Tests/OR (Hearing OR Hearing loss OR Tinnitus OR Dizziness OR Vertigo OR Ataxia OR Balance OR Inner ear OR Cochlea OR Vestibule OR Labyrinth OR Hearing test OR Audiometry OR Audiogram OR Otoacoustic Emission* OR Evoked Potential* OR Caloric Test* OR Electronystagmography OR Vestibulo-Ocular reflex OR Vestibular Function Test* OR Otoprotect* OR Ototoxic*),ti,ab.
3. AND 2
4. Limit 3 to (English language and yr="1987-Current")

EMBASE

1. Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR Anticholesteremic Agents/ OR Hypercholesterolemia/ OR Hyperlipidemia/ OR simvastatin/ OR Atorvastatin Calcium/ OR Rosuvastatin Calcium/ OR Pravastatin/ OR Lovastatin/ OR (Hydroxymethylglutaryl-CoA Reductase Inhibitor* OR Anticholesteremic agent* OR Hypolipidemic agent* OR Cholesterol lowering agent* OR Antilipid agent* OR Antilipemic agent* OR Antilipidemic agent* OR Hypolipidemic agent* OR Lipid lowering agent* OR Statin OR Simvastatin OR Atorvastatin OR Rosuvastatin OR Pravastatin OR Lovastatin OR Fluvastatin OR Pitavastatin),ti,ab.
PRAYUENYONG ET AL.

2. Hearing/OR Hearing loss/OR Tinnitus/OR Dizziness/OR Vertigo/OR Ataxia/OR Ear, inner/OR Cochlea/OR Vestibule, labyrinth/OR Hearing test/OR Audiometry/OR Otoacoustic Emissions/OR Evoked Potentials, Auditory/OR Evoked Potentials, Auditory, Brain Stem/OR Caloric Tests/OR Electronystagmography/OR Reflex, Vestibulo-Ocular/OR Vestibular Function Tests/OR (Hearing OR Hearing loss OR Tinnitus OR Dizziness OR Vertigo OR Ataxia OR Balance OR Inner ear OR Cochlea OR Vestibule OR Labyrinth OR Hearing test OR Audiometry OR Otoacoustic Emission* OR Evoked Potential* OR Caloric Test* OR Electronystagmography OR Vestibulo-Ocular reflex OR Vestibular Function Test* OR Otoprotect* OR Ototoxic*).
t,ab.
3. 1 AND 2
4. Limit 3 to (English Language and EMBASE and Exclude MEDLINE Journals and YR="1978‐Current")

International pharmaceutical abstracts

1. Hydroxymethylglutaryl-CoA Reductase Inhibitors/OR Anticholesteremic Agents/OR Hypolipidemic Agents/OR simvastatin/OR Atorvastatin Calcium/OR Rosuvastatin Calcium/OR Pravastatin/OR Lovastatin/OR (Hydroxymethylglutaryl-CoA Reductase Inhibitor* OR Anticholesteremic agent* OR Hypolipidemic agent* OR Cholesterol lowering agent* OR Antilipid agent* OR Antilipemic agent* OR Antilipidemic agent* OR Hypolipidemic agent* OR Lipid lowering agent* OR Statin OR Simvastatin OR Atorvastatin OR Rosuvastatin OR Pravastatin OR Lovastatin OR Fluvastatin OR Pitavastatin) OR ab(Hydroxymethylglutaryl-CoA Reductase Inhibitor* OR Anticholesteremic agent* OR Hypolipidemic agent* OR Cholesterol lowering agent* OR Antilipid agent* OR Antilipemic agent* OR Antilipidemic agent* OR Hypolipidemic agent* OR Lipid lowering agent* OR Statin OR Simvastatin OR Atorvastatin OR Rosuvastatin OR Pravastatin OR Lovastatin OR Fluvastatin OR Pitavastatin)

2. Hearing/OR Hearing loss/OR Tinnitus/OR Dizziness/OR Vertigo/OR Ataxia/OR Ear, inner/OR Cochlea/OR Vestibule, labyrinth/OR Hearing test/OR Audiometry/OR Otoacoustic Emissions/OR Evoked Potentials, Auditory/OR Evoked Potentials, Auditory, Brain Stem/OR Caloric Tests/OR Electronystagmography/OR Reflex, Vestibulo-Ocular/OR Vestibular Function Tests/OR (Hearing OR Hearing loss OR Tinnitus OR Dizziness OR Vertigo OR Ataxia OR Balance OR Inner ear OR Cochlea OR Vestibule OR Labyrinth OR Hearing test OR Audiometry OR Otoacoustic Emission* OR Evoked Potential* OR Caloric Test* OR Electronystagmography OR Vestibulo-Ocular reflex OR Vestibular Function Test* OR Otoprotect* OR Ototoxic*).ti,ab.
3. 1 AND 2
4. Limit 3 to (English Language and YR="1978‐Current")

ClinicalTrials.gov

Study Type: All
Study Results: All
Status: Studies: All
Intervention/Treatment: HMG-CoA Reductase Inhibitor OR Statin OR Simvastatin OR Atorvastatin OR Rosuvastatin OR Pravastatin OR Lovastatin OR Fluvastatin OR Pitavastatin
Outcome Measures: Hearing OR Tinnitus OR Dizziness OR Vertigo OR Ataxia OR Audiometry OR Otoacoustic Emissions OR Evoked Potentials OR Caloric Tests OR Electronystagmography OR Vestibular Function Tests OR Inner Ear

Proquest dissertations & theses A&I

Proquest dissertations & theses A&I

Narrowed by: Language: English
Limited to 1978 to 2018

Google scholar

Statin AND otoprotection