Brazilian Journal of Biology®

ISSN 1519-6984 (Print)
ISSN 1678-4375 (Online)

Original Article

Plant-based therapies for gentamicin-induced ototoxicity: experimental evidence and pharmacological insights

Terapias à base de plantas na ototoxicidade induzida por gentamicina: abordagens experimentais e perspectivas farmacológicas

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Abstract

Gentamicin is an aminoglycoside antibiotic widely used in clinical practice, but its administration may lead to ototoxicity, resulting in cochlear and vestibular damage. Experimental studies have investigated the potential of medicinal plants and their bioactive compounds to prevent or mitigate this toxicity. This integrative review critically analyses preclinical evidence on the protective and therapeutic effects of medicinal plants and their derivatives in animal models of gentamicin-induced ototoxicity. Studies published between 1995 and 2025 were selected from the PubMed, Web of Science, and ScienceDirect databases. The main findings indicate that species such as Ginkgo biloba, Panax ginseng, Salvia miltiorrhiza, Nigella sativa, and Pyrola rotundifolia exert protective, preventive, and regenerative effects through antioxidant and anti-inflammatory mechanisms. These effects are mainly related to the reduction of oxidative stress, modulation of inflammation, and preservation of sensory cell integrity. The evidence supports the pharmacological potential of natural compounds for the prevention and treatment of ototoxicity.

Keywords: gentamicin, ototoxicity, medicinal plants, animal models, oxidative stress.

Resumo

A gentamicina é um antibiótico aminoglicosídeo amplamente utilizado na prática clínica, porém seu uso pode causar ototoxicidade, resultando em danos cocleares e vestibulares. Estudos experimentais têm investigado o potencial de plantas medicinais e seus compostos bioativos na prevenção ou mitigação desses efeitos tóxicos. Esta revisão integrativa analisa criticamente as evidências pré-clínicas sobre os efeitos protetores e terapêuticos de plantas medicinais e seus derivados em modelos animais de ototoxicidade induzida por gentamicina. Foram selecionados estudos publicados entre 1995 e 2025 nas bases de dados PubMed, Web of Science e ScienceDirect. Os principais resultados indicam que espécies como Ginkgo biloba, Panax ginseng, Salvia miltiorrhiza, Nigella sativa e Pyrola rotundifolia exercem efeitos protetores, preventivos e regenerativos por meio de mecanismos antioxidantes e anti-inflamatórios. Esses efeitos estão relacionados principalmente à redução do estresse oxidativo, modulação da inflamação e preservação da integridade das células sensoriais. As evidências reforçam o potencial farmacológico de compostos naturais para a prevenção e o tratamento da ototoxicidade.

Palavras-chave: gentamicina, ototoxicidade, plantas medicinais, modelos animais, estresse oxidativo.

1. Introduction

Medicinal plants and their phytocompounds have attracted increasing interest due to their therapeutic potential, widely associated with antioxidant, anti-inflammatory, and cytoprotective properties. These mechanisms are particularly relevant in clinical conditions characterized by oxidative stress and cellular apoptosis, such as drug-induced ototoxicity (Ansari et al., 2025; Riaz et al., 2023).

Ototoxicity is defined as functional and structural alterations in the auditory and/or vestibular systems resulting from exposure to chemical agents, which can lead to irreversible manifestations such as hearing loss, tinnitus, and vertigo (Greguske et al., 2021; Sedó-Cabezón et al., 2014). Among the most well-known ototoxic agents are aminoglycoside antibiotics, whose use revolutionized the treatment of severe infections but brought significant adverse effects. Historically, concerns arose from the use of streptomycin and dihydrostreptomycin in tuberculosis treatment, when the first reports of drug-induced hearing loss were described (Guthrie, 2008; Schacht, 1998).

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Received: November 6, 2025 – Accepted: January 19, 2026
Editor: Takako Matsumura Tundisi

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Currently, gentamicin (GM) is one of the most widely used aminoglycosides, especially in the treatment of Gram-negative bacterial infections (Tian et al., 2013). Despite its efficacy, prolonged use is associated with important adverse effects, including nephrotoxicity and ototoxicity, the latter characterized by hearing loss, tinnitus, and, in some cases, vertigo due to vestibular impairment (Yang et al., 2011). These manifestations are related to the selective destruction of sensory hair cells (HCs) and inner ear neurons (Ruan et al., 2014a). Initially, GM predominantly affects outer hair cells (OHCs) in the basal turn of the cochlea; at higher doses, it also damages inner hair cells (IHCs), and nerve fibers can be injured independently of HC status (Ruan et al., 2014a; Somdaş et al., 2015).

Aminoglycoside-induced ototoxicity involves complex mechanisms, including mitochondrial oxidative stress, activation of pro-inflammatory pathways, and caspase-3-mediated apoptosis (Hong et al., 2025; Kim et al., 2023). Substances capable of neutralizing reactive oxygen species (ROS) or stimulating endogenous antioxidant systems represent promising candidates for preventing or treating this adverse effect.

Given the absence of specific pharmacological therapies to mitigate ototoxic damage, alternative strategies have been investigated, including the use of natural compounds. Several medicinal plants and their derivatives have demonstrated efficacy in modulating oxidative stress and protecting hair cells in experimental models. Notably, some of these species have a traditional use history in communities for treating auditory disorders or inflammation, strengthening the ethnopharmacological relevance of their investigation.

Therefore, understanding the efficacy of these phytotherapeutics and their mechanisms of action is essential for developing safe and effective approaches. This integrative review aims to critically analyze the available evidence on the effects of medicinal plants and their derivatives in animal models of gentamicin-induced ototoxicity, highlighting the main compounds, their preventive, protective, and regenerative mechanisms, and gaps for future research.

2. Materials and Methods

2.1. Search strategy

An integrative review was conducted through a comprehensive search of the scientific literature using electronic databases, including PubMed, Web of Science, ScienceDirect, Scopus, and Springer, considering publications up to August 2025. Given the specificity of the topic and the limited number of records with uniform descriptors, varied search strategies were applied, combining controlled descriptors (MeSH/DeCS) and free keywords. The literature search was performed using different terms, including "medicinal plants", "phytotherapy", "ototoxicity", "animal model", "experimental models", "gentamicin", "aminoglycosides", "vestibulotoxicity", and "vestibular dysfunction", among others.

After applying the inclusion and exclusion criteria, 27 articles were selected that met the objectives of this review (Figure 1).

2.2. Eligibility criteria and study selection

This integrative review followed systematized procedures to ensure transparency in the selection and analysis of the included studies. Inclusion and exclusion criteria were defined based on the scope and objectives of the present review.

Studies were included if they simultaneously met the following criteria: experimental investigations using animal models (in vivo) exposed to gentamicin; interventions with medicinal plants, plant extracts, or natural compounds; and evaluation of ototoxicity and vestibular dysfunction through behavioral, histological, functional, or electrophysiological tests (Table 1).

Exclusion criteria were: studies involving human subjects, in vitro models, or literature reviews; studies in which the tested treatment did not involve plants, phytocompounds, or natural derivatives; and studies with incomplete or duplicate data or methodologies that did not allow the extraction of relevant information for this review.

3. Results

A total of 27 studies on the use of medicinal plants or plant-derived compounds in gentamicin (GM) induced ototoxicity in animal models were identified. Of these, 8 studies addressed vestibulotoxicity, with emphasis on vestibular dysfunction, and 19 studies investigated cochleotoxicity. The publications spanned the period from 1995 to 2025.

Rodents were the most frequently used models, with a predominance of Sprague-Dawley rats, generally exposed to GM via intraperitoneal (IP) administration at doses ranging from 100 to 160 mg/kg for 10 to 15 days. To a lesser extent, studies employed Wistar rats under similar protocols, as well as BALB/c or C57BL/6J mice, using higher doses (100–400 mg/kg). Models using guinea pigs were also reported, varying in route of administration (IM, IP, or IT) and duration (1 to 14 days).

This variability in species, doses, and administration routes reflects differences in experimental objectives and model sensitivity, which limits direct comparison across studies.

The included studies employed different approaches to assess gentamicin-induced ototoxicity and vestibular function. Vestibular function was investigated through behavioral and motor reflex tests, such as Rotarod, tail suspension, swimming, and balance tests, among others, which allowed the identification of alterations in postural control and motor coordination.

Auditory function and cochlear alterations were examined using electrophysiological and morphological methods, including electrocochleography, auditory brainstem responses, otoacoustic emissions, and histological analyses by electron or confocal microscopy. In addition, immunohistochemical and molecular techniques were employed to investigate apoptosis and the integrity of hair cells.

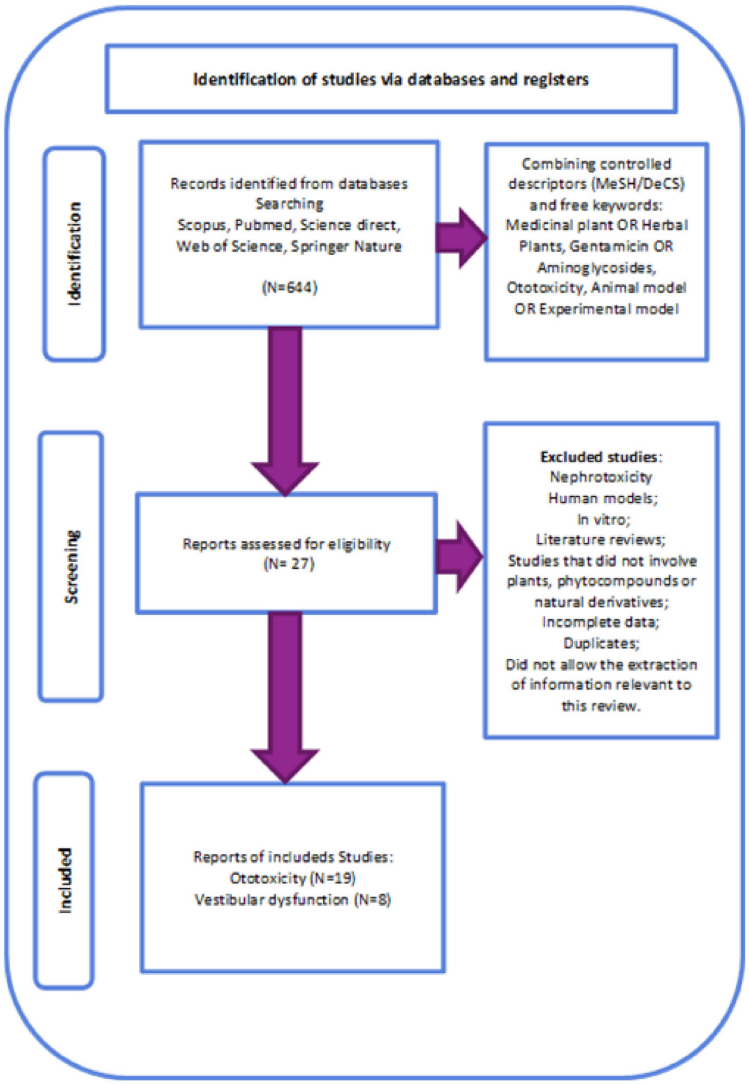


Figure 1. Schematic diagram of selected articles from databases and the manual search process.

Overall, the studies combined behavioral tests, electrophysiological analyses, and histopathological approaches, providing a comprehensive characterization of gentamicin-induced vestibular and auditory dysfunctions across different animal models.

Several medicinal plants and natural compounds have demonstrated protective, preventive, and regenerative effects against gentamicin-induced ototoxicity. Among the most extensively investigated agents are Ginkgo biloba, Panax ginseng, Curcuma longa, and Nigella sativa, whose extracts or active constituents exhibited antioxidant, anti-inflammatory, and neuroprotective properties capable of preserving hair cell integrity and improving vestibulocochlear function.

Some studies also reported regenerative effects, particularly with compounds such as quercetin, naringenin, and rutin, which promoted tissue repair and reduced apoptosis. Taken together, the evidence indicates that different phytochemicals — including flavonoids, polyphenols, and antioxidant vitamins — exert significant benefits in preventing and mitigating gentamicin-induced damage.

Table 2 summarizes the plants, bioactive compounds, and main effects observed in the evaluated experimental models.

4. Discussion

4.1. Experimental models

The reviewed studies employed different experimental models, with variations in species, strain, sex, and age of the animals. These differences influence sensitivity to gentamicin (GM) and require dose adjustments to achieve consistent induction of ototoxicity, since doses effective in rats do not always produce the same effect in mice or guinea pigs (L. Chen et al., 2012; Sinswat et al., 2000). Moreover, the pharmacokinetics of GM in the inner ear

Table 1. Medicinal plants and phytochemicals tested against gentamicin-induced ototoxicity in experimental animal models.

Author (Year)	Animal model	GM dose	Plant/extract	Main focus (V, VC, C)	Parameters evaluated	Main findings
(Xuan et al., 1995)	Guinea pigs	160 mg/k IM (10d)	*Pyrola rotundifolia L. & Astragalus membranaceus*	C	ECochG, SEM	Protects cochlea against ototoxic lesions
(Jung et al., 1998)	Guinea pigs	5 mg/kg IT 2 groups 45 min; 2 groups 24 h	*Ginkgo biloba*	C	ECochG, SEM	Cochlear protective effect
(Fetoni et al., 2003)	Guinea pigs	100 mg/k IM (14d)	Alpha-tocopherol (Vitamin E)	VC	Vestibular function; ECochG; CAP; Morphological evaluation	Prevents otovestibular toxicity
(Fetoni et al., 2004)	Guinea pigs	100 mg/k IM (14d)	Alpha-tocopherol (Vitamin E)	C	ECochG; CAP; SEM	Protects hair cells and auditory/ vestibular function
(Long et al., 2004)	Guinea pigs	100 mg/k IM (14d)	*Drynaria fortunei* (Kunze)	C	ABR; Histological analysis; SEM	Prevents ototoxicity and repairs hair cells
(Yang et al., 2011)	Guinea pigs	10–80 mg/ml IT (1d)	*Ginkgo biloba*	C	ABR; Cochlear apoptosis assessment	Reduces apoptosis and ROS formation in cochlea
(Choung et al., 2011)	Male SD rats	100 mg/kg or 160 mg/kg IP (5, 10 or 14 d)	Korean ginseng (*Panax ginseng*)	VC	Rotarod; ABR; SEM	Protects against hearing loss and hair cell death
(Uzun et al., 2012)	Male Wistar rats	120 mg/kg IP (16 d)	Garlic (*Allium sativum*)	C	BERA	Attenuates GM-induced hearing loss
(Tian et al., 2013)	Female SD rats	IT on alternate days (2 weeks), 20 µl/rat	Red ginseng (*Panax ginseng*)	VC	Head tilt; Tail suspension; Swimming test; ABR; SEM; Cell culture and viability assays	Protects cochleo-vestibular function and hair cells, inhibiting apoptosis
(Shi et al., 2014)	Guinea pigs	100 mg/kg IP (10 d)	*Salvia miltiorrhiza*	C	ABR; SEM	Reverses apoptosis and necrosis in cochlea, preventing ototoxicity
(Sagit et al., 2014)	Female SD rats	120 mg/kg IP (15 d)	Thymoquinone (*Nigella sativa*)	C	ABR; Histomorphological analysis (TUNEL and immunohistochemistry)	Prevents ototoxicity
(Kahya et al., 2014)	Female Wistar albino rats	160 mg/kg IM (5 d)	Pomegranate extract (*Punica granatum*)	C	OAE; Chemiluminescence	Significant protective effect against GM-induced ototoxicity
(Sagit et al., 2015)	Female SD rats	120 mg/kg IP (14 d)	Quercetin (Flavonoid)	C	ABR; Histomorphological analysis (TUNEL and immunohistochemistry)	Attenuates cochlear lesions and ABR thresholds
(Uzun et al., 2016)	Male Wistar rats	120 mg/kg IP (25 d)	Garlic (*Allium sativum*)	C	BERA	Attenuates hearing loss, potentially reduces vestibular dysfunction
(Edizer et al., 2017)	Male SD rats	120 mg/kg IP (14 d)	*Nigella sativa*	C	ABR; Histological examination	Partially prevents hearing loss

Notes: SD = Sprague-Dawley; V = vestibular function; C = cochlear function; VC = cochleo-vestibular function; ECochG = electrocochleography; ABR = Auditory Brainstem Response; SEM = Scanning Electron Microscopy; BERA = Brainstem Evoked Response Audiometry; DPOAE = Distortion Product Otoacoustic Emission; CAP = Compound Action Potential. Doses follow the original protocols (IM = intramuscular; IP = intraperitoneal; IT = intratympanic); d = days.

Table 1. Continued...

Author (Year)	Animal model	GM dose	Plant/extract	Main focus (V, VC, C)	Parameters evaluated	Main findings
(Koçak et al., 2017)	Male SD rats	120 mg/kg IP (14 d)	Naringenin (Flavonoid)	C	OAE; ABR	Mitigates ototoxicity
(Kaplan et al., 2017)	BALB/c mice	100 mg/kg IP (9 d)	Alpha-linolenic acid	VC	Rotarod; Histological analysis	Prevents ototoxicity by inhibiting apoptosis and inflammation
(Haryuna et al., 2018)	Male Wistar albino rats	Single IT dose of GM(40 mg/ml) (1-3 d)	Curcumin (*Curcuma longa*)	C	Immunohistochemical analysis	Prevents and reduces apoptotic index
(Salcan et al., 2021)	Male Wistar albino rats	100 mg/kg IP (14 d)	Rutin (Flavonoid)	C	Histopathological and biochemical evaluations	May be useful for treating ototoxicity
(Niu et al., 2021)	Male C57BL/6J mice	200 mg/kg IP (7 d)	Puerarin (*Pueraria phaseoloides*)	C	ABR; Histological assays	Protects cochlear hair cells, reduces ROS and mitochondrial apoptosis
(Abd-Elhakim et al., 2021)	SD rats	120 mg/kg IP (15 d)	Curcumin (*Curcuma longa*)	V	Swimming performance; Water maze working memory; Forced swimming test; Open field test; Histopathological evaluations	Protects vestibular function via antioxidant actions
(Haryuna et al., 2021)	Male Wistar albino rats	Single IT dose of GM (40 mg/ml) (1-3 d)	Curcumin (*Curcuma longa*)	C	Immunohistochemical analysis	Prevents and reduces oxidative stress
(Abd-Elhakim et al., 2022)	SD rats	120 mg/kg IP (15 d)	Curcumin (*Curcuma longa*)	VC	Beam balance; Grasp reflex; Startle response; Histopathological and immunohistochemical evaluations	Protects cochleo-vestibular function, modulating apoptotic and inflammatory pathways
(Tuna and Tüzemen, 2023)	SD rats	120 mg/kg IP (10 d)	*Nigella sativa*	C	ABR	Prevents ototoxicity prophylactically and therapeutically
(Kinoshita et al., 2023)	Guinea pigs	0,4 mg/mL, 0,2 ml IT (14 d)	7,8-Dihydroxyflavone (Flavonoid)	V	Caloric test; Histological analysis; Confocal microscopy	Promotes hair cell regeneration and vestibular function
(Tuna and Tüzemen, 2024)	Male SD rats	120 mg/kg IP (10 d)	*Nigella sativa*	C	ABR	Reverses ototoxic effects
(Jiang et al., 2024)	C57BL/6J mice	400 mg/kg, IP (14 d)	Gastrodin (*Gastrodia elata*)	VC	Contact reflex; Swimming test; Air-righting reflex; Cellular and molecular assays	Prevents vestibular lesions

Notes: SD = Sprague-Dawley; V = vestibular function; C = cochlear function; VC = cochleo-vestibular function; ECochG = electrocochleography; ABR = Auditory Brainstem Response; SEM = Scanning Electron Microscopy; BERA = Brainstem Evoked Response Audiometry; DPOAE = Distortion Product Otoacoustic Emission; CAP = Compound Action Potential. Doses follow the original protocols (IM = intramuscular; IP = intraperitoneal; IT = intratympanic); d = days.

Table 2. Summary of the effects of medicinal plants and natural compounds on protection, prevention, and regeneration of gentamicin-induced ototoxicity

Plant/Compound	Protective Effect	Preventive Effect	Regenerative/ Curative Effect	References
Pyrola rotundifolia L. & Astragalus membranaceus	✓	X	X	(Xuan et al., 1995)
Ginkgo biloba	✓	X	X	(Jung et al., 1998)
Alpha-tocopherol (Vitamin E)	✓	X	X	(Fetoni et al., 2003)
Alpha-tocopherol (Vitamin E)	X	✓	X	(Fetoni et al., 2004)
Drynaria fortunei (Kunze)	X	✓	✓	(Long et al., 2004)
Ginkgo biloba	X	✓	✓	(Yang et al., 2011)
Korean ginseng (*Panax ginseng*)	✓	X	X	(Choung et al., 2011)
Garlic (*Allium sativum*)	X	X	✓	(Uzun et al., 2012)
Red ginseng (*Panax ginseng*)	✓	X	X	(Tian et al., 2013)
Salvia miltiorrhiza	X	X	✓	(Shi et al., 2014)
Thymoquinone (*Nigella sativa*)	X	✓	X	(Sagit et al., 2014)
Pomegranate extract (*Punica granatum*)	✓	X	X	(Kahya et al., 2014)
Quercetin (Flavonoid)	X	X	✓	(Sagit et al., 2015)
Garlic (*Allium sativum*)	X	X	✓	(Uzun et al., 2016)
Nigella sativa	X	✓	X	(Edizer et al., 2017)
Naringenin (Flavonoid)	X	X	✓	(Koçak et al., 2017)
Alpha-linolenic acid	X	✓	X	(Kaplan et al., 2017)
Curcumin (*Curcuma longa*)	X	✓	X	(Haryuna et al., 2018)
Rutin (Flavonoid)	X	X	✓	(Salcan et al., 2021)
Puerarin (*Pueraria phaseoloides*)	✓	X	X	(Niu et al., 2021)
Curcumin (*Curcuma longa*)	✓	X	X	(Abd-Elhakim et al., 2021)
Curcumin (*Curcuma longa*)	X	✓	X	(Haryuna et al., 2021)
Curcumin (*Curcuma longa*)	✓	X	X	(Abd-Elhakim et al., 2022)
Nigella sativa	X	✓	X	(Tuna and Tüzemen, 2023)
7,8-Dihydroxyflavone (Flavonoid)	X	X	✓	(Kinoshita et al., 2023)
Nigella sativa	X	✓	X	(Tuna and Tüzemen, 2024)
Gastrodin (*Gastrodia elata*)	X	✓	X	(Jiang et al., 2024)

Legend: ✓ = present; X = absent.

vary according to species and experimental conditions, which affects the dose required to induce ototoxic injury (Blunston et al., 2015; Federspil et al., 1976).

As observed in the results, Sprague-Dawley rats were the most commonly used model, generally subjected to intraperitoneal (IP) administration of 100 to 120 mg/kg for 10 to 15 days. This dosage range is widely recognized as effective for inducing ototoxicity, as demonstrated in comparative studies (Somdaş et al., 2015; Blunston et al., 2015; Talaat et al., 2025). Thus, these protocols represent a robust experimental model for testing agents with therapeutic potential.

Despite the predominance of male rats, some studies included females, although no controlled comparisons between sexes have been reported (Koçak et al., 2017; Tuna and Tüzemen, 2023, 2024; Sagit et al., 2015; Tian et al., 2013). This methodological gap, combined with the lack of standardization in doses and routes of administration, underscores the need for more consistent protocols to improve the reproducibility and translational applicability of the findings.

The Wistar strain generally follows the same dosage pattern adopted for Sprague-Dawley rats, although variations in exposure time are observed (Uzun et al., 2012, 2016), Salcan et al., 2021). This flexibility reflects differences in experimental objectives. For example, Aydemir et al. (2022) administered 120 mg/kg of GM intraperitoneally (IP) for 14 days to evaluate the protective effect of caffeic acid phenethyl ester (CAPE), while Aydin et al. (2012) applied the same dose for 7 days and also achieved successful induction of ototoxicity. In contrast, Lopez-Gonzalez et al.

(2000) used 160 mg/kg via intramuscular injection for 7 days, reinforcing the variability among protocols.

In addition, the intratympanic (IT) route was widely employed, particularly in studies focused on evaluating vestibular dysfunctions (Erkoç et al., 2023; Güneri et al., 2017; Vural et al., 2017).

Although this review identified few studies using plants and their derivatives in mice, these animals are widely used in research involving gene therapies and ototoxic agents, showing heterogeneity in routes of administration, dosages, and experimental models (Hui et al., 2022; Li et al., 2016; Pfannenstiel et al., 2009) . Examples include the BALB/c model, treated with 100 mg/kg for nine days (Kaplan et al., 2017), and the C57BL/6J model, subjected to 200 mg/kg for seven days (Niu et al., 2021) or 400 mg/kg for 14 days (Jiang et al., 2024).

It is observed that higher doses of GM are required to induce vestibular dysfunction in mice, as vestibular cells exhibit greater resistance to the antibiotic, accumulate lower amounts of the drug, and require stronger activation of toxic pathways to produce functional impairment. This behavior contrasts with the higher sensitivity of cochlear cells, which sustain damage even at lower doses (Kinoshita et al., 2023; Liu et al., 2015; Sultemeier and Hoffman, 2017).

Guinea pigs were the models that showed the greatest variation in administration route, dose, and exposure time. Several studies standardized the use of GM to induce ototoxicity in this model, reporting consistent outcomes such as significant hearing loss and cochlear hair cell damage. Among the routes evaluated, the most frequently used were intramuscular (IM) and intraperitoneal (IP), generally with lower doses than those employed in rats and mice, averaging 100 mg/kg (Fetoni et al., 2003, 2004; Long et al., 2004; Shi et al., 2014), administered for periods of 10 to 14 days. In one of the analyzed studies, a dose of 160 mg/kg via IM was administered for 10 days (Xuan et al., 1995). Higher doses, such as 160 mg/kg/day for 7 days, accelerate hearing loss but are not required to ensure consistent induction of ototoxicity (Turan et al., 2017). Thus, the data indicate that a dose of 100 mg/kg is sufficient to induce robust and reproducible ototoxicity in guinea pigs.

The lack of uniformity in gentamicin doses across studies represents a significant challenge for comparing results. While some protocols used lower doses for shorter periods, others employed higher and more prolonged administrations, reflecting different experimental objectives. This variation can directly affect the magnitude of vestibular or cochlear injury, as well as the observed efficacy of the tested compounds. Thus, the absence of standardization hinders the establishment of comparable parameters and highlights the need to define more consistent dose ranges in future experimental models of ototoxicity.

Some selected studies also employed the intratympanic (IT) route to induce ototoxicity (Jung et al., 1998; Kinoshita et al., 2023). This approach stands out as a relevant alternative for experimental models, as it allows detailed investigation of the cellular and molecular mechanisms involved in ototoxicity, including the production of reactive oxygen species, apoptosis, and enzymatic alterations (Heinrich et al., 2006; Takumida et al., 1999). Moreover, it enables the analysis of gentamicin accumulation patterns in different cochlear and vestibular cell types, revealing differences in susceptibility and intracellular transport (Heinrich et al., 2015). Another important aspect is that local application provides greater reproducibility and control over the dose effectively delivered to the inner ear, facilitating comparisons across studies (Hibi et al., 2001).

Differences among experimental models and dosing protocols also influence the interpretation of the protective effects of the studied compounds. Animals of different strains or ages may respond differently to the same ototoxic agent, altering the magnitude of the observed effect (Chen, 2019; Jodynis-liebert & Kujawska, 2020). Likewise, variations in dose, timing of inoculation, or duration of exposure to the tested compounds may determine whether the observed effect is predominantly protective, preventive, or regenerative (Calabrese, 2016; Chesler et al., 2022). These factors underscore the need to carefully consider experimental conditions when comparing results across studies and suggest that fine-tuning of dose and model is essential to optimize therapeutic efficacy in future research on ototoxicity (Jiang et al., 2024; Maroto et al., 2021).

The assessment of vestibular function is still scarcely and inconsistently explored. Among the included studies, nine employed behavioral tests - such as observation of posture, balance, gait, and reflexes (e.g., the righting reflex) - to detect vestibular dysfunction in a sensitive and noninvasive manner (Abd-Elhakim et al., 2021, 2022; Choung et al., 2011; Fetoni et al., 2003; Jiang et al., 2024; Kaplan et al., 2017; Kinoshita et al., 2023; Tian et al., 2013; Uzun et al., 2016). Although useful, results may vary depending on the evaluator's training, strain, and experimental conditions (Fetoni et al., 2003; Jiang et al., 2024).

Gentamicin induces progressive vestibular injury through the destruction of sensory hair cells, resulting in stable deficits in balance and postural reflexes, which can be measured using balance, righting, and swimming tests (Maroto et al., 2021; Jiang et al., 2024).

Behavioral tests have demonstrated sensitivity in detecting vestibular deficits and, when combined with morphological analyses, provide a robust functional assessment. However, methodological heterogeneity — including test selection, scoring criteria, and experimental conditions — limits direct comparability across studies (Abd-Elhakim et al., 2021, 2022; Choung et al., 2011; Jiang et al., 2024; Kaplan et al., 2017; Kinoshita et al., 2023; Tian et al., 2013).

Tests such as Rotarod, swimming, head tilt, and tail suspension are widely employed with semi-quantitative scoring scales, whereas specific procedures (e.g., the caloric test) enable evaluation of the vestibulo-ocular reflex (Kinoshita et al., 2023; Güneri et al., 2017; Hui et al., 2022).

Complementarily, studies have integrated electrophysiological, histological, and biochemical techniques (ECochG, SEM, immunohistochemistry, oxidative markers), which allow for the correlation of structural alterations with functional deficits and a deeper understanding of the mechanisms of action of the tested compounds (Fetoni et al., 2004; Tian et al., 2014; Edizer et al., 2017).

4.2. Effects of medicinal plants and phytocompounds in experimental models

Medicinal plants and their derivatives have shown consistent protective effects against gentamicin-induced ototoxicity, acting both preventively and reparatively. In different experimental models, these compounds reduced the severity of lesions and promoted functional and structural recovery of the vestibular system (Kinoshita et al., 2023; Salcan et al., 2021). The main benefits observed include improvements in balance and motor coordination, as well as partial preservation or regeneration of the sensory cells within the labyrinth.

The underlying mechanisms are mainly related to the modulation of oxidative stress and inflammation, involving the neutralization of reactive oxygen species, stimulation of endogenous antioxidant defenses, and inhibition of apoptotic and necrotic pathways (Abd-Elhakim et al., 2022; Haryuna et al., 2021). Some compounds also exhibit regenerative effects on cochlear and vestibular structures, further reinforcing their therapeutic potential (Choung et al., 2011; Jiang et al., 2024; Sagit et al., 2014). Altogether, these findings support the role of such substances as promising pharmacological candidates for the prevention and recovery of vestibular dysfunctions associated with ototoxicity.

4.2.1. Plants and compounds with protective effects

Experimental studies have identified several plant species and natural compounds with potential protective effects against gentamicin (GM)-induced ototoxicity. Among them, *Pyrola rotundifolia L.* and *Astragalus membranaceus* (Xuan et al., 1995), *Ginkgo biloba* (Jung et al., 1998), and red ginseng (*Panax ginseng*), whose active component ginsenoside Rb1 demonstrated both cellular and behavioral protection by preventing hair cell loss and preserving vestibular function after GM exposure (Choung et al., 2011; Tian et al., 2013) stand out. Other relevant compounds include puerarin, derived from *Pueraria phaseoloides* (Niu et al., 2021), curcumin, the main polyphenol of turmeric (Abd-Elhakim et al., 2021, 2022), and alpha-tocopherol (vitamin E), which also showed protective effects (Fetoni et al., 2003).

Most of these agents share antioxidant and anti-inflammatory mechanisms. They reduce oxidative stress by decreasing the production of reactive oxygen species (ROS), the main mediators of cellular damage (Shi et al., 2014; H. Yang et al., 2024; Zhang et al., 2024). In addition, many compounds modulate proteins involved in apoptosis, reducing the activation of caspase-3, BAX, and p53, while increasing the expression of anti-apoptotic proteins such as BCL-2, thereby protecting auditory and vestibular cells (Hong et al., 2025; Kim et al., 2023; Niu et al., 2021). Some also act on the regulation of intracellular signaling pathways associated with cell survival and tissue regeneration (Hong et al., 2025; Niu et al., 2021; Yang et al., 2011; Zhang et al., 2024). These protective effects, demonstrated by behavioral and histological studies, indicate a promising potential for preventive and therapeutic strategies against GM-induced ototoxicity.

4.2.2. Plants and compounds with preventive effects

Plants and compounds that demonstrated preventive effects against gentamicin (GM)-induced ototoxicity mainly include species with recognized antioxidant and neuroprotective activity. Among them, Drynaria fortunei (Kunze) stands out, evaluated for its potential to reduce oxidative stress and preserve cells (Long et al., 2004). Ginkgo biloba also showed consistent results in attenuating vestibular damage, attributed to its sensory antioxidant and anti-inflammatory activity (Yang et al., 2011). Nigella sativa proved promising in studies using both the whole extract (Edizer et al., 2017; Tuna and Tüzemen, 2023, 2024) and its main bioactive component, thymoquinone (Sagit et al., 2014), showing protective effects on sensory cells and vestibular structures. Another relevant phytocompound is gastrodin, derived from Gastrodia elata, recently associated with the modulation of antioxidant and anti-apoptotic pathways, demonstrating preventive potential against vestibular damage as assessed by behavioral tests (Jiang et al., 2024).

In addition to plants, isolated bioactive compounds such as alpha-linolenic acid have shown promising results in preventing ototoxicity by inhibiting apoptosis and inflammation (Kaplan et al., 2017). Alpha-tocopherol (vitamin E) has also demonstrated preventive efficacy (Fetoni et al., 2004), reinforcing the role of redox balance in protection against ototoxic injury.

4.2.3. Plants and compounds with regenerative or curative effects

Among the substances evaluated, some demonstrated regenerative or curative effects against gentamicin-induced damage. Notable examples include Drynaria fortunei (Kunze) (Kunze) (Long et al., 2004) , Ginkgo biloba (Yang et al., 2011), Salvia miltiorrhiza (Shi et al., 2014) and garlic (Allium sativum) (Uzun et al., 2012, 2016). In addition, several flavonoids, such as quercetin (Sagit et al., 2015), naringenin (Koçak et al., 2017), rutin (Salcan et al., 2021) and 7,8-dihydroxyflavone (Kinoshita et al., 2023) also showed potential to promote tissue regeneration and reversal of vestibular damage.

The flavonoid 7,8-dihydroxyflavone, a TrkB agonist, was shown to promote hair cell regeneration, preservation of the vestibular nerve, and synaptic remodeling, resulting in recovery of vestibular function after GM treatment (Kinoshita et al., 2023). The proposed mechanisms include antioxidant action, modulation of apoptotic and inflammatory pathways, and stimulation of survival and regeneration of sensory cells in the inner ear.

4.2.4. Underlying mechanisms and multifunctional properties

In experimental models, plant-derived compounds preserved cellular integrity and improved performance in balance and coordination tests, indicating consistent functional effects. Some exhibited multifunctional properties, with simultaneous preventive and regenerative actions (Long et al., 2004; Yang et al., 2011), reinforcing their therapeutic potential against gentamicin (GM)-induced ototoxicity.

The curative and regenerative effects observed after GM exposure mainly involve the restoration of cellular functions, inhibition of apoptosis, and modulation of antioxidant pathways (Choung et al., 2011; Jiang et al., 2024; Sagit et al., 2014), The mechanisms of action include direct

neutralization of reactive oxygen species, stimulation of endogenous defenses (such as antioxidant enzymes and cell survival factors), and modulation of inflammatory and apoptotic pathways, all of which contribute to the preservation of auditory and vestibular functions.

Despite these promising findings, important limitations remain. Most experimental studies continue to focus primarily on nephrotoxicity, whereas ototoxicity - and particularly vestibular dysfunction - has been comparatively underexplored. In addition, heterogeneity in experimental models, outcome measures, and treatment protocols hampers direct comparisons across studies and limits clinical extrapolation.

An important source of variability among the studies analyzed in this review concerns the extraction methods used to obtain plant-derived compounds. Different extraction approaches, such as aqueous and ethanolic methods, may substantially influence the concentration, stability, and bioavailability of active metabolites, including flavonoids and polyphenols such as quercetin and curcumin. Experimental studies in rodent models have demonstrated that extraction protocols directly affect the chemical profile and biological activity of plant extracts, which may impact the interpretation of effective doses and protective outcomes (Bati et al., 2023; Macorini et al., 2022; Marinho et al., 2022). These findings underscore the need for caution when comparing results derived from different extraction procedures and distinct phytochemical compositions.

In this context, although in vivo experimental models are widely employed to investigate the cellular and molecular effects of bioactive substances under conditions of chemically induced toxicity, most studies rely on the direct administration of these compounds in animal models. This approach does not fully account for pharmacokinetic challenges in humans, particularly those related to bioavailability and penetration across the blood–labyrinth barrier (Bomfim et al., 2022). Furthermore, variability in gentamicin dosing protocols - ranging from 100 to 160 mg/kg - is known to influence the severity of ototoxic injury and may affect the magnitude of the protective effects attributed to plant-based therapies (Ruan et al., 2014b; Sedó-Cabezón et al., 2014; Somdaş et al., 2015). Collectively, these factors highlight the need for standardized experimental protocols, careful consideration of extraction methodologies, and pharmacokinetic-oriented approaches to enhance the translational relevance and therapeutic potential of plant-derived compounds in the prevention and treatment of aminoglycoside-induced ototoxicity.

5. Conclusion

The reviewed studies demonstrate that medicinal plants and their derivatives exert protective (e.g., *Pyrola rotundifolia L., Astragalus membranaceus, Ginkgo biloba, Panax ginseng*), preventive (*Drynaria fortunei, Nigella sativa*), and regenerative (*Salvia miltiorrhiza, Allium sativum*) effects in experimental models of ototoxicity. These actions are primarily associated with the modulation of oxidative stress, attenuation of inflammation, and preservation of the structural integrity of sensory cells within the inner ear. Despite the heterogeneity among gentamicin-induced ototoxicity models and administration protocols, the findings collectively reinforce the therapeutic potential of these agents and underscore the need for future studies to standardize experimental designs and further elucidate their mechanisms of action, paving the way for safe and effective clinical applications.

Acknowledgements

The first author thanks the Coordination for the Improvement of Higher Education Personnel – Brazil (CAPES) for supporting her through a doctoral fellowship in the Graduate Program in Health and Development in the Central-West Region at the Federal University of Mato Grosso do Sul. We also extend our gratitude to the National Council for Scientific and Technological Development (CNPq) and the Financing Agency for Studies and Projects (FINEP).

Data Availability Statement

No new data were generated or analyzed in this study.

References

ABD-ELHAKIM, Y.M., ABDEL-MOTAL, S.M., MALHAT, S.M., MOSTAFA, H.I., IBRAHIM, W.M., BEHEIRY, R.R., MOSELHY, A.A.A. and SAID, E.N., 2022. Curcumin attenuates gentamicin and sodium salicylate ototoxic effects by modulating the nuclear factor-kappaB and apoptotic pathways in rats. *Environmental Science and Pollution Research International*, vol. 29, no. 60, pp. 89954-89968. https://doi.org/10.1007/s11356-022-21932-1. PMid:35859240.

ABD-ELHAKIM, Y.M., ABDEL-MOTAL, S.M., MALHAT, S.M., MOSTAFA, H.I., MOSELHY, A.A.A., BEHEIRY, R.R. and SAID, E.N., 2021. Curcumin mitigates neurotoxic and neurobehavioral changes of gentamicin and sodium salicylate in rats by adjusting oxidative stress and apoptosis. *Life Sciences*, vol. 265, pp. 118824. https://doi.org/10.1016/j.lfs.2020.118824. PMid:33278387.

ANSARI, P., REBERIO, A.D., ANSARI, N.J., KUMAR, S., KHAN, J.T., CHOWDHURY, S., EL-MORDY, F.M.A., HANNAN, J.M.A., FLATT, P.R., ABDEL-WAHAB, Y.H.A. and SEIDEL, V., 2025. Therapeutic potential of medicinal plants and their phytoconstituents in diabetes, cancer, infections, cardiovascular diseases, inflammation and gastrointestinal disorders. *Biomedicines*, vol. 13, no. 2, pp. 454. https://doi.org/10.3390/biomedicines13020454. PMid:40002867.

AYDEMIR, F., ULKU, C.H., ELMAS, C. and SEYMEN, C.M., 2022. Analysis of potential protective effects of caffeic acid phenethyl ester against gentamicin ototoxicity: an experimental study. *Iranian Journal of Basic Medical Sciences*, vol. 25, no. 1, pp. 121-125. https://doi.org/10.22038/IJBMS.2022.60794.13467. PMid:35656452.

AYDIN, E., AYDOG, F., TAŞTAN, E., IRIZ, A., KARACA, G. and CAN, I.H., 2012. Are systemic voriconazole and caspofungin ototoxic? An experimental study with rats. *Clinical and Experimental Otorhinolaryngology*, vol. 5, no. 3, pp. 145-149. https://doi.org/10.3342/ceo.2012.5.3.145. PMid:22977711.

BATI, B., CELIK, I., VURAN, N.E., TURAN, A., ALKAN, E.E. and ZIREK, A.K., 2023. Effects of Gundelia tournefortii L. on biochemical parameters, antioxidant activities and DNA damage in a rat model of experimental obesity. *Brazilian Journal of Biology*, vol. 83, pp. e251198. https://doi.org/10.1590/1519-6984.251198.

BLUNSTON, M.A., YONOVITZ, A., WOODAHL, E.L. and SMOLENSKY, M.H., 2015. Gentamicin-induced ototoxicity and nephrotoxicity vary with circadian time of treatment and entail separate mechanisms. *Chronobiology International*, vol. 32, no. 9, pp. 1223-1232. https://doi.org/10.3109/07420528.2015.1082483 . PMid:26506922.

BOMFIM, E.M.S., COELHO, A.A.O.P., SILVA, M.C., MARQUES, E.J. and VALE, V.L.C., 2022. Phytochemical composition and biological activities of extracts from ten species of the family Melastomataceae Juss. *Brazilian Journal of Biology*, vol. 82, pp. e242112. https://doi.org/10.1590/1519-6984.242112. PMid:34133563.

CALABRESE, E.J., 2016. Preconditioning is hormesis part II: how the conditioning dose mediates protection: Dose optimization within temporal and mechanistic frameworks. *Pharmacological Research*, vol. 110, pp. 265-275. https://doi.org/10.1016/j.phrs.2015.12.020. PMid:26748033.

CHEN, C., 2019. Impact of dosing schedule in animal experiments on compound progression decisions. *Drug Discovery Today*, vol. 24, no. 2, pp. 371-376. https://doi.org/10.1016/j.drudis.2018.11.006. PMid:30448352.

CHEN, L., XIONG, S., LIU, Y. and SHANG, X., 2012. Effect of different gentamicin dose on the plasticity of the ribbon synapses in cochlear inner hair cells of C57BL/6J mice. *Molecular Neurobiology*, vol. 46, no. 2, pp. 487-494. https://doi.org/10.1007/s12035-012-8312-7. PMid:22865193.

CHESLER, K.C., MOTZ, C.T., BALES, K.L., ALLEN, R.A., VO, H.K. and PARDUE, M.T., 2022. Voluntary oral dosing for precise experimental compound delivery in adult rats. *Laboratory Animals*, vol. 56, no. 2, pp. 147-156. https://doi.org/10.1177/00236772211016926. PMid:34392713.

CHOUNG, Y.H., KIM, S.W., TIAN, C., MIN, J.Y., LEE, H.K., PARK, S.N., LEE, J.B. and PARK, K., 2011. Korean red ginseng prevents gentamicin-induced hearing loss in rats. *The Laryngoscope*, vol. 121, no. 6, pp. 1294-1302. https://doi.org/10.1002/lary.21756.

EDIZER, D.T., YIGIT, O., CINAR, Z., GUL, M., KARA, E., YIGITCAN, B., HAYIR, D. and ATAS, A., 2017. Protective role of intratympanic nigella sativa oil against gentamicin induced hearing loss. *International Journal of Pediatric Otorhinolaryngology*, vol. 97, pp. 83-88. https://doi.org/10.1016/j.ijporl.2017.03.034. PMid:28483257.

ERKOÇ, E., ÇETIN, A.Ç., DURANKAYA, S.M., MIÇILI, S.Ç., KESKINOĞLU, P., YILMAZ, O., KIRKIM, G. and GÜNERI, E.A., 2023. Effects of Cross-linked Hyaluronic Acid in a Rat Model of Vestibular and Cochlear Toxicity. *Turkish Archives of Otorhinolaryngology*, vol. 61, no. 3, pp. 124-133. https://doi.org/10.4274/tao.2023.2023-5-14. PMid:38020411.

FEDERSPIL, P., SCHÄTZLE, W. and TIESLER, E., 1976. Pharmacokinetics and Ototoxicity of Gentamicin, Tobramycin, and Amikacin. *The Journal of Infectious Diseases*, vol. 134, suppl. 1, pp. S200-S205. https://doi.org/10.1093/infdis/134.Supplement_1.S200. PMid:972282.

FETONI, A.R., SERGI, B., FERRARESI, A., PALUDETTI, G. and TROIANI, D., 2004. α-Tocopherol protective effects on gentamicin ototoxicity: an experimental study. *International Journal of Audiology*, vol. 43, no. 3, pp. 166-171. https://doi.org/10.1080/14992020400050023. PMid:15198381.

FETONI, A.R., SERGI, B., SCARANO, E., PALUDETTI, G., FERRARESI, A. and TROIANI, D., 2003. Protective effects of α-tocopherol against gentamicin-induced oto-vestibulo toxicity: an experimental study. *Acta Oto-Laryngologica*, vol. 123, no. 2, pp. 192-198. https://doi.org/10.1080/00016480310001484. PMid:12701739.

GREGUSKE, E.A., LLORENS, J. and PYOTT, S.J., 2021. Assessment of cochlear toxicity in response to chronic 3,3′-iminodipropionitrile in mice reveals early and reversible functional loss that precedes overt histopathology. *Archives of Toxicology*, vol. 95, no. 3, pp. 1003-1021. https://doi.org/10.1007/s00204-020-02962-5. PMid:33495873.

GÜNERI, E.A., OLGUN, Y., ASLIER, M., NUTI, D., KIRKIM, G., MUNGAN, S., KOLATAN, E., AKTAŞ, S., TRABALZINI, F., ELLIDOKUZ, H., YILMAZ, O. and MANDALA, M., 2017. Cochlear and Vestibular Effects of Combined Intratympanic Gentamicin and Dexamethasone. *The Journal of International Advanced Otology*, vol. 13, no. 1, pp. 47-52. https://doi.org/10.5152/iao.2016.2181. PMid:28084995.

GUTHRIE, O.W., 2008. Aminoglycoside induced ototoxicity. *Toxicology*, vol. 249, no. 2-3, pp. 91-96. https://doi.org/10.1016/j.tox.2008.04.015. PMid:18514377.

HARYUNA, T.S.H., FAUZIAH, D., ANGGRAINI, S., HARAHAP, M.P.H. and HARAHAP, J., 2021. Antioxidant effect of curcumin on the prevention of oxidative damage to the cochlea in an ototoxic rat model based on malondialdehyde expression. *International Archives of Otorhinolaryngology*, vol. 26, no. 1, pp. e119-e124. https://doi.org/10.1055/s-0040-1722161. PMid:35096168.

HARYUNA, T.S.H., PURBA, A.H.W., FARHAT, F. and ALVIANDI, W., 2018. The antiapoptotic effect of curcumin in the fibroblast of the cochlea in an ototoxic rat model. *Iranian Journal of Otorhinolaryngology*, vol. 30, no. 100, pp. 247-253. https://doi.org/10.22038/ijorl.2018.26701.1871. PMid:30245978.

HEINRICH, U.R., SCHMIDTMANN, I., STRIETH, S. and HELLING, K., 2015. Cell-specific accumulation patterns of gentamicin in the guinea pig cochlea. *Hearing Research*, vol. 326, pp. 40-48. https://doi.org/10.1016/j.heares.2015.03.010. PMid:25882166.

HEINRICH, U.R., SELIVANOVA, O., BRIEGER, J. and MANN, W.J., 2006. Endothelial nitric oxide synthase upregulation in the cochlea of the guinea pig after intratympanic gentamicin injection. *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, vol. 263, no. 1, pp. 62-68. http://doi.org/10.1007/s00405-005-0949-7.

HIBI, T., SUZUKI, T. and NAKASHIMA, T., 2001. Perilymphatic concentration of gentamicin administered intratympanically in guinea pigs. *Acta Oto-Laryngologica*, vol. 121, no. 3, pp. 336-341. https://doi.org/10.1080/000164801300102699. PMid:11425197.

HONG, S., HAN, E., PARK, S., HYUN, K., LEE, Y., BAEK, H.W., KIM, H.-J., RAH, Y.C. and CHOI, J., 2025. Protective effects of (-)-butaclamol against gentamicin-induced ototoxicity: in vivo and in vitro approaches. *International Journal of Molecular Sciences*, vol. 26, no. 9, pp. 4201. https://doi.org/10.3390/ijms26094201. PMid:40362438.

HUI, J., LEI, Q., JI, Z. and ZI, D., 2022. Betahistine alleviates benign paroxysmal positional vertigo (BPPV) through inducing production of multiple CTRP family members and activating the ERK1/2-AKT/PPARγ pathway. *Biological Research*, vol. 55, no. 1, pp. 16. https://doi.org/10.1186/s40659-022-00385-3. PMid:35379352.

JIANG, W., LI, F., XU, H., CAO, M., XIAO, B., GONG, K., MA, J., ZHANG, W., TANG, X., LIU, F. and YU, S., 2024. Protective effects of gastrodin against gentamicin-induced vestibular damage by the notch signaling pathway. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology*, vol. 45, no. 9, pp. 1059-1067. https://doi.org/10.1097/MAO.0000000000004250. PMid:39264922.

JODYNIS-LIEBERT, J. and KUJAWSKA, M., 2020. Biphasic dose-response induced by phytochemicals: experimental evidence. *Journal of Clinical Medicine*, vol. 9, no. 3, pp. 718. https://doi.org/10.3390/jcm9030718. PMid:32155852.

JUNG, H.W., CHANG, S.O., KIM, C.S., RHEE, C.S. and LIM, D.H., 1998. Effects of Ginkgo biloba extract on the cochlear damage induced by local gentamicin installation in guinea pigs. *Journal of Korean Medical Science*, vol. 13, no. 5, pp. 525-528. https://doi.org/10.3346/jkms.1998.13.5.525. PMid:9811183.

KAHYA, V., OZUCER, B., DOGAN, R., MERIC, A., YUKSEL, M., GEDIKLI, O. and OZTURAN, O., 2014. Pomegranate extract: a potential protector against aminoglycoside ototoxicity. *The Journal of Laryngology, Rhinology, and Otology*, vol. 128, no. 1, pp. 43-48. https://doi.org/10.1017/S0022215113003460. PMid:24451682.

KAPLAN, H.M., ŞINGIRIK, E., ERDOĞAN, K.E. and DORAN, F., 2017. Protective effect of alpha-linolenic acid on gentamicin-induced ototoxicity in mice. *Somatosensory & Motor Research*, vol. 34, no. 3, pp. 145-150. https://doi.org/10.1080/08990220.2017.1356283. PMid:28760048.

KIM, Y.R., BAEK, J.I., LEE, K.Y. and KIM, U.K., 2023. Berberine chloride protects cochlear hair cells from aminoglycoside-induced ototoxicity by reducing the accumulation of mitochondrial reactive oxygen species. *Free Radical Biology & Medicine*, vol. 204, pp. 177-183. https://doi.org/10.1016/j.freeradbiomed.2023.04.017. PMid:37119862.

KINOSHITA, M., FUJIMOTO, C., IWASAKI, S., KONDO, K. and YAMASOBA, T., 2023. Oral Administration of TrkB Agonist, 7, 8–Dihydroxyflavone Regenerates Hair Cells and Restores Function after Gentamicin–Induced Vestibular Injury in Guinea Pig. *Pharmaceutics*, vol. 15, no. 2, pp. 493. https://doi.org/10.3390/pharmaceutics15020493. PMid:36839815.

KOÇAK, İ., SARAC, S., AYDOGAN, E., ŞENTÜRK, E., AKAKIN, D., KOROGLU, K. and ÖZER, Ö.F., 2017. Evaluation of the possible protective role of naringenin on gentamicin-induced ototoxicity: a preliminary study. *International Journal of Pediatric Otorhinolaryngology*, vol. 100, pp. 247-253. https://doi.org/10.1016/j.ijporl.2017.07.008. PMid:28802382.

LI, S., HANG, L. and MA, Y., 2016. FGF22 protects hearing function from gentamycin ototoxicity by maintaining ribbon synapse number. *Hearing Research*, vol. 332, pp. 39-45. https://doi.org/10.1016/j.heares.2015.11.011. PMid:26639016.

LIU, J., KACHELMEIER, A., DAI, C., LI, H. and STEYGER, P.S., 2015. Uptake of fluorescent gentamicin by peripheral vestibular cells after systemic administration. *PLoS One*, vol. 10, no. 3, pp. e0120612. https://doi.org/10.1371/journal.pone.0120612. PMid:25793391.

LONG, M., SMOUHA, E.E., QIU, D., LI, F., JOHNSON, F. and LUFT, B., 2004. Flavanoid of Drynaria fortunei protects against gentamicin ototoxicity. *Phytotherapy Research : PTR*, vol. 18, no. 8, pp. 609-614. https://doi.org/10.1002/ptr.1505. PMid:15476311.

LOPEZ-GONZALEZ, M.A., GUERRERO, J.M., TORRONTERAS, R., OSUNA, C. and DELGADO, F., 2000. Ototoxicity caused by aminoglycosides is ameliorated by melatonin without interfering with the antibiotic capacity of the drugs. *Journal of Pineal Research*, vol. 28, no. 1, pp. 26-33. https://doi.org/10.1034/j.1600-079x.2000.280104.x. PMid:10626598.

MACORINI, L.F.B., MARIS, R.S., TEIXEIRA, T.C., ITO, C.N.A., KURAOKA-OLIVEIRA, A.M., BACHA, F.B., MEJIA, A.J.B., SALVADOR, M.J., KASSUYA, C.A.L. and ARENA, A.C., 2022. Preclinical safety evaluation of the ethanolic extract from the aerial parts of Gomphrena celosioides Mart. in rodents. *Regulatory Toxicology and Pharmacology : RTP*, vol. 133, pp. 105217. https://doi.org/10.1016/j.yrtph.2022.105217. PMid:35792246.

MARINHO, T.A., OLIVEIRA, M.G., MENEZES-FILHO, A.C.P., CASTRO, C.F.S., OLIVEIRA, I.M.M., BORGES, L.L., MELO-REIS, P.R. and SILVA-JR, N.J., 2022. Phytochemical characterization, and antioxidant and antibacterial activities of the hydroethanolic extract of *Anadenanthera peregrina* stem bark. *Brazilian Journal of Biology*, vol. 82, pp. e234476. https://doi.org/10.1590/1519-6984.234476. PMid:33681898.

MAROTO, A.F., BARRALLO-GIMENO, A. and LLORENS, J., 2021. Relationship between vestibular hair cell loss and deficits in two anti-gravity reflexes in the rat. *Hearing Research*, vol. 410, pp. 108336. https://doi.org/10.1016/j.heares.2021.108336. PMid:34481267.

NIU, P., SUN, Y., WANG, S., LI, G., TANG, X., SUN, J., PAN, C. and SUN, J., 2021. Puerarin alleviates the ototoxicity of gentamicin by inhibiting the mitochondria-dependent apoptosis pathway. *Molecular Medicine Reports*, vol. 24, no. 6, pp. 851. https://doi.org/10.3892/mmr.2021.12491. PMid:34651662.

PFANNENSTIEL, S.C., PRAETORIUS, M., PLINKERT, P.K., BROUGH, D.E. and STAECKER, H., 2009. Bcl-2 Gene Therapy Prevents Aminoglycoside-Induced Degeneration of Auditory and Vestibular Hair Cells. *Audiology & Neuro-Otology*, vol. 14, no. 4, pp. 254-266. https://doi.org/10.1159/000192953. PMid:19151550.

RIAZ, M., KHALID, R., AFZAL, M., ANJUM, F., FATIMA, H., ZIA, S., RASOOL, G., EGBUNA, C., MTEWA, A.G., UCHE, C.Z. and ASLAM, M.A., 2023. Phytobioactive compounds as therapeutic agents for human diseases: a review. *Food Science & Nutrition*, vol. 11, no. 6, pp. 2500-2529. https://doi.org/10.1002/fsn3.3308. PMid:37324906.

RUAN, Q., AO, H., HE, J., CHEN, Z., YU, Z., ZHANG, R., WANG, J. and YIN, S., 2014a. Topographic and quantitative evaluation of gentamicin-induced damage to peripheral innervation of mouse cochleae. *Neurotoxicology*, vol. 40, pp. 86-96. https://doi.org/10.1016/j.neuro.2013.11.002. PMid:24308912.

RUAN, Q., AO, H., HE, J., CHEN, Z., YU, Z., ZHANG, R., WANG, J. and YIN, S., 2014b. Topographic and quantitative evaluation of gentamicin-induced damage to peripheral innervation of mouse cochleae. *Neurotoxicology*, vol. 40, pp. 86-96. https://doi.org/10.1016/j.neuro.2013.11.002. PMid:24308912.

SAGIT, M., KORKMAZ, F., GÜRGEN, S.G., GUNDOGDU, R., AKCADAG, A. and OZCAN, I., 2015. Quercetine attenuates the gentamicin-induced ototoxicity in a rat model. *International Journal of Pediatric Otorhinolaryngology*, vol. 79, no. 12, pp. 2109-2114. https://doi.org/10.1016/j.ijporl.2015.09.023. PMid:26434546.

SAGIT, M., KORKMAZ, F., GÜRGEN, S.G., KAYA, M., AKCADAG, A. and OZCAN, I., 2014. The protective role of thymoquinone in the prevention of gentamicin ototoxicity. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery*, vol. 35, no. 5, pp. 603-609. https://doi.org/10.1016/j.amjoto.2014.07.002.

SALCAN, İ., DILBER, M., BAYRAM, R., SÜLEYMAN, E., YAZICI, G.N., ÇOBAN, A. and SÜLEYMAN, H., 2021. Effect of rutin on gentamicin-induced ototoxicity in rats: a biochemical and histopathological examination. *ENT Updates*, vol. 11, no. 1, pp. 8-13. https://doi.org/10.5152/entupdates.2021.887158.

SCHACHT, J., 1998. Aminoglycoside ototoxicity: prevention in sight? *Otolaryngology - Head and Neck Surgery*, vol. 118, no. 5, pp. 674-677. https://doi.org/10.1177/019459989811800518. PMid:9591868.

SEDÓ-CABEZÓN, L., BOADAS-VAELLO, P., SOLER-MARTÍN, C. and LLORENS, J., 2014. Vestibular damage in chronic ototoxicity: A mini-review. *Neurotoxicology*, vol. 43, pp. 21-27. https://doi.org/10.1016/j.neuro.2013.11.009. PMid:24333467.

SHI, L., AN, Y., WANG, A., GAO, Q. and YANG, Y., 2014. The protective effect of Salvia miltiorrhiza on gentamicin-induced ototoxicity. *American Journal of Otolaryngology*, vol. 35, no. 2, pp. 171-179. https://doi.org/10.1016/j.amjoto.2013.08.022. PMid:24119490.

SINSWAT, P., WU, W.J., SHA, S.H. and SCHACHT, J., 2000. Protection from ototoxicity of intraperitoneal gentamicin in guinea pig. *Kidney International*, vol. 58, no. 6, pp. 2525-2532. https://doi.org/10.1046/j.1523-1755.2000.00437.x. PMid:11115087.

SOMDAŞ, M.A., KORKMAZ, F., GURGEN, S.G., SAGIT, M. and AKCADAĞ, A., 2015. N-acetylcysteine prevents gentamicin ototoxicity in a rat model. *The Journal of International Advanced Otology*, vol. 11, no. 1, pp. 12-18. https://doi.org/10.5152/iao.2015.650. PMid:26223711.

SULTEMEIER, D.R. and HOFFMAN, L.F., 2017. Partial aminoglycoside lesions in vestibular epithelia reveal broad sensory dysfunction associated with modest hair cell loss and afferent calyx retraction. *Frontiers in Cellular Neuroscience*, vol. 11, pp. 284767. https://doi.org/10.3389/fncel.2017.00331. PMid:29163044.

TAKUMIDA, M., POPA, R. and ANNIKO, M., 1999 [viewed 6 November 2025]. Free radicals in the guinea pig inner ear following gentamicin exposure. *ORL* [online], vol. 61, no. 1, pp. 63-70. Available from: http://karger.com/orl/article-pdf/61/2/63/3378843/000027643.pdf.

TALAAT, A., BADR, N.S., GHONEIM, A.Z. and EL-SAIDY, S.A., 2025. Antioxidant efficiency of Sarcophyton crude extract against gentamicin toxicity in male albino rats. *Scientific Reports*, vol. 15, no. 1, pp. 7468. https://doi.org/10.1038/s41598-025-90316-5. PMid:40032912.

TIAN, C., KIM, Y.J., LIM, H.J., KIM, Y.S., PARK, H.Y. and CHOUNG, Y.H., 2014. Red ginseng delays age-related hearing and vestibular dysfunction in C57BL/6 mice. *Experimental Gerontology*, vol. 57, pp. 224-232. https://doi.org/10.1016/j.exger.2014.06.013. PMid:24952098.

TIAN, C.J., KIM, S.W., KIM, Y.J., LIM, H.J., PARK, R., SO, H.S. and CHOUNG, Y.H., 2013. Red ginseng protects against gentamicin-induced balance dysfunction and hearing loss in rats through antiapoptotic functions of ginsenoside Rb1. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*, vol. 60, pp. 369-376. https://doi.org/10.1016/j.fct.2013.07.069. PMid:23933362.

TUNA, B. and TÜZEMEN, G., 2023. Protective effects of nigella sativa oil against gentamicin-induced ototoxicity in rats: A dose-ranging study. *International Journal of Pediatric Otorhinolaryngology*, vol. 164, pp. 111405. https://doi.org/10.1016/j.ijporl.2022.111405. PMid:36481814.

TUNA, B. and TÜZEMEN, G., 2024. Is Gentamicin-Induced Ototoxicity Reversible with Delayed Administration of Nigella Sativa Oil? An Experimental Study. *Turkish Journal of Ear Nose and Throat*, vol. 34, no. 2, pp. 37-41. https://doi.org/10.26650/Tr-ENT.2024.1426956.

TURAN, M., CIĞER, E., ARSLANOĞLU, S., BÖREKCI, H. and ÖNAL, K., 2017. Could edaravone prevent gentamicin ototoxicity? An experimental study. *Human & Experimental Toxicology*, vol. 36, no. 2, pp. 123-127. https://doi.org/10.1177/0960327116639360. PMid:27022163.

UZUN, L., BALBALOGLU, E. and AKINCI, H., 2012. Garlic-Supplemented Diet Attenuates Gentamicin-Induced Ototoxicity: An Experimental Study. *The Annals of Otology, Rhinology, and Laryngology*, vol. 121, no. 2, pp. 139-143. https://doi.org/10.1177/000348941212100211. PMid:22397224.

UZUN, L., KOKTEN, N., CAM, O.H., KALCIOGLU, M.T., UGUR, M.B., TEKIN, M. and ACAR, G.O., 2016. The Effect of Garlic Derivatives (S-Allylmercaptocysteine, Diallyl Disulfide, and S-Allylcysteine) on Gentamicin Induced Ototoxicity: An Experimental Study. *Clinical and Experimental Otorhinolaryngology*, vol. 9, no. 4, pp. 309-313. https://doi.org/10.21053/ceo.2015.01032. PMid:27136366.

VURAL, A., ŞAHIN, M.İ., AYDIN, M., GÜNDOĞDU, R., ARLI, T., OKUDUCU, H., DIZDAR, D. and KÜLAHLI, İ., 2017. The effect of nystatin solution on otoacoustic emissions in rats. *The Journal of International Advanced Otology*, vol. 13, no. 1, pp. 105-109. https://doi.org/10.5152/iao.2016.1667. PMid:27819649.

XUAN, W., DONG, M. and DONG, M., 1995. Effects of Compound Injection Of Pyrola Rotundifolia L and astragalus membranaceus Bge on experimental guinea pigs' gentamicin ototoxicity. *The Annals of Otology, Rhinology, and Laryngology*, vol. 104, no. 5, pp. 374-380. https://doi.org/10.1177/000348949510400507. PMid:7747908.

YANG, H., ZONG, T., LIU, J., WANG, D., GONG, K., YIN, H., ZHANG, W., XU, T. and YANG, R., 2024. Rutin Attenuates Gentamycin-induced Hair Cell Injury in the Zebrafish Lateral Line via Suppressing STAT1. *Molecular Neurobiology*, vol. 61, no. 11, pp. 9548-9561. https://doi.org/10.1007/s12035-024-04179-4. PMid:38653908.

YANG, T.H., YOUNG, Y.H. and LIU, S.H., 2011. EGb 761 (Ginkgo biloba) protects cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis. *The Journal of Nutritional Biochemistry*, vol. 22, no. 9, pp. 886-894. https://doi.org/10.1016/j.jnutbio.2010.08.009. PMid:21190826.

ZHANG, Y., YU, S., GUO, X., WANG, L., YU, L. and WANG, P., 2024. Therapeutic potential of salidroside in preserving rat cochlea organ of corti from gentamicin-induced injury through modulation of NRF2 signaling and GSK3β/NF-κB pathway. *PLoS One*, vol. 19, no. 3, pp. e0298529. https://doi.org/10.1371/journal.pone.0298529. PMid:38483863.