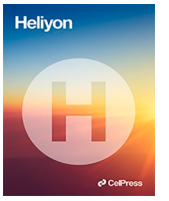
Heliyon 9 (2023) e22422

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Traditional Chinese medicine for the prevention and treatment of presbycusis

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ARTICLE INFO

Keywords:
Traditional Chinese medicine
Age-related hearing loss
Presbycusis
Mechanism

ABSTRACT

Background: Presbycusis/Age-related hearing loss is a sensorineural hearing loss caused by age-related deterioration of the auditory system that poses a risk to the physical and mental health of older people, including social and cognitive decline. It is also associated with frailty, falls and depression. There are currently no specific medications for the treatment of presbycusis, and early detection and intervention are key to its prevention and management. Traditional Chinese medicine interventions may offer opportunities in the prevention and treatment of presbycusis, but there is no relevant review.

Methods: Literature searches was conducted using PubMed, Cochrane Library, Web of Science, and China National Knowledge Infrastructure (CNKI) databases for review articles, research articles, clinical trials, meta-analyses, and case studies in animal models and clinical trials.

Results: We summarized the pathological mechanisms associated with presbycusis, related to genetic factors, environment, lifestyle, and molecular mechanisms related to oxidative stress, mitochondrial dysfunction, and inflammatory pathways. It is suggested that traditional Chinese medicine interventions may offer opportunities in the prevention and treatment of presbycusis using active ingredients of herbs or formulas, acupuncture, and exercise such as Tai Chi Chuan or Ba Duan Jin. The active ingredients of herbs or formulas may exert ear protection through Nrf2-mediated antioxidant pathways, NF-kB and NLRP3-related anti-inflammatory signaling, and regulation of autophagy.

Conclusions: Here, we review the pathogenetic factors and pathological mechanisms involved in presbycusis, as well as traditional Chinese medicine interventions and treatments, with the aim of providing a new perspective for the prevention and treatment of hearing loss in the elderly and further improving their quality of life.

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https://doi.org/10.1016/j.heliyon.2023.e22422
Received 25 July 2023; Received in revised form 10 November 2023; Accepted 13 November 2023
Available online 28 November 2023

1. Introduction

The World Report on Hearing 2021 estimates that more than 1.5 billion people already have varying degrees of hearing loss, which could increase to 2.5 billion by 2050. The global prevalence of moderate or greater hearing loss increases with age, affecting more than 58 % of adults over 60 years of age, and the prevalence of some degree of hearing loss among males (5.6 %) is slightly higher than that among females (5.5 %) [1]. Although this sensory disorder is not life threatening in the older population, it affects the psychosocial well-being and quality of life of individuals. Increasing evidence links falls, social isolation and depression, and cognitive impairment with loss of hearing [2–4]. Recent studies have identified age-related hearing loss (ARHL) as a high-risk factor for cognitive decline, including dementia and Alzheimer's disease (AD) [5–7]. It therefore represents a significant social and economic burden that is increasing with current demographic changes.

Presbycusis, also known as ARHL, is a sensorineural hearing loss (SNHL) caused by degeneration of the auditory system with increasing age [8]. It is a progressive, bilateral, symmetrical hearing loss, and its hearing curve is mostly slope-shaped at higher frequencies and sometimes flat [9]. Historical studies have shown that there are six pathological types of presbycusis: sensory, neural, metabolic, cochlear conductive, mixed, and indeterminate. These involve alterations in many auditory structures, including degeneration of cochlear hair cells, vascular striae atrophy, and degeneration of the auditory nerve [10,11]. Until now, the etiology of presbycusis remains unclear. Some studies showed that oxidative stress, apoptosis, mtDNA mutations and autophagy are involved in the progression of presbycusis [12–14].

Up until recently, there were no therapeutic treatments available to save the dying cochlear hair cells and SGNs or to replenish these cells once they had been lost. To prevent or reverse the presbycusis, however, great efforts have been undertaken to find innovative therapies. Due to its lengthy history of preventing and postponing age-related disorders, Traditional Chinese Medicine (TCM) is seen as a potential resource. The primary causes of presbycusis and how it is treated by TCM will be outlined in this review, which will serve as a resource or inspiration for future studies on presbycusis and TCM.

2. Methodology

The literature search was conducted using PubMed, Cochrane Library, Web of Science, and China National Knowledge Infrastructure (CNKI) databases, using the keywords "presbycusis, " "age-related hearing loss, " "age-related deafness, " "aging, " and "ageing, " "traditional Chinese medicine, " "traditional medicine, " "herbal medicine, " "medicinal plants, " "plants, " "ethnopharmacology, " and

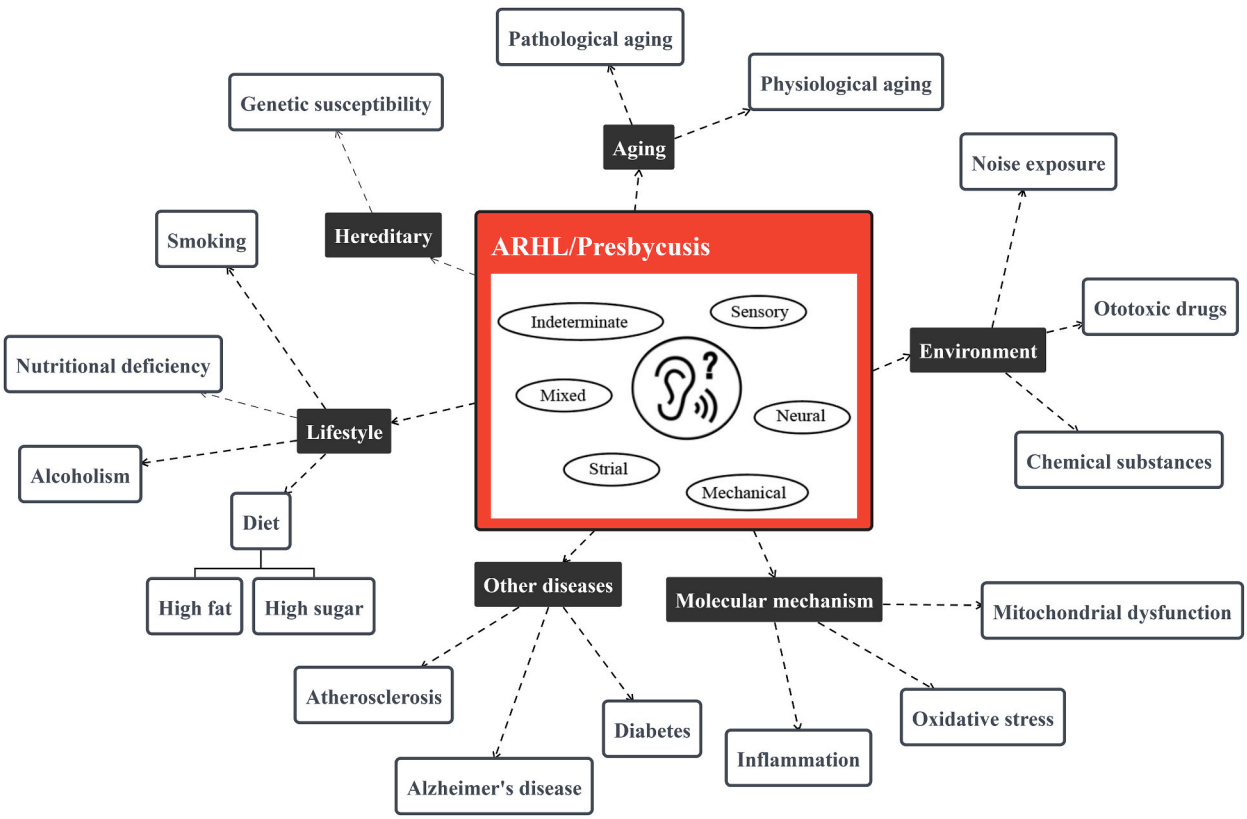

Fig. 1. Influencing factors involved in the pathogenesis of presbycusis.

"ethnomedicine ". Boolean operators 'OR' and 'AND' were used to narrow and target the search. The inclusion criteria were as follows: articles published in the last 15 years for review articles, research articles, clinical trials, meta-analyses, and case studies.

3. Pathogenetic factors and pathological mechanisms of presbycusis

The occurrence and development of presbycusis are multifactorial. In addition to age-related degeneration, other contributing factors, such as genetic factors, the environment, lifestyle, and diseases of other organ systems, can accelerate the progression of presbycusis (Fig. 1).

3.1. Genetic factors for presbycusis

Hearing loss is genetically heterogeneous, and there are approximately 1000 different pathogenic genes, of which 140 have been shown to cause human deafness [15,16]. The genetic architecture of age-related hearing impairment (ARHI) has recently been revealed by genome-wide association analysis, which found that carriers of rare ARHI variants were at higher risk according to the ARHI Genetic Risk Score (GRS), and that rare variants were more likely to develop severe ARHI than combinations of common GRS variants [17]. Genetic factors can also influence hearing loss among middle-aged and elderly in the middle and high frequencies, with heritability of approximately 40–55 % for PTA and better ear hearing level at 2, 4, 8 and 12.5 kHz in 358 twins and 1 triplet (mean age 51.55 years) studied [18]. In addition, many new epigenetic markers have been identified that contribute to further understanding the pathological mechanisms underlying presbycusis. In a clinical study, elevated levels of methylation at the CpG site of Cadherin 23 gene were found to correlate with ARHI in the peripheral blood of 50 women aged 50–75 years with presbycusis [19]. Animal experiments have shown that deletion of *Ceacam16* accelerates age-related tectorial membrane degeneration in the mouse cochlea, and the extent of this degeneration depends on the genetic background [20]. Hearing loss is a common symptom in individuals harboring inherited mitochondrial DNA (mtDNA) mutations. In the inner ear of mitochondrial mutator mice ($Polg^{mut/mut}$), mtDNA deletions accumulate significantly with increasing age [21]. BAK1 gene expression and BAK1/BCL2 ratio in peripheral blood may be biomarkers for Iranian presbycusis [22]. CCR3 and GILZ genes may be biomarkers for Chinese presbycusis subjects by our previous research [23]. The relationship between miRNAs and presbycusis was discovered by Jianguo Tang's research group. They summarized the following miRNAs as miRNA-183, miRNA-181a, miR-34a, Let-7 family, miR-29b/SIRT1/PGC-1α,95 and 60 miRNAs may be important for the presbycusis [13].

3.2. Environmental factors for presbycusis

Multiple genetic factors are inextricably linked to the risk of various diseases, and environmental factors exacerbate this risk. A previous study showed that presbycusis and noise-induced hearing loss are determined by the interaction between environmental and genetic factors [24]. The risk of hearing loss in different work environments is related to the level of noise exposure and hearing protective equipment, with the highest risk of hearing loss in industry, shipbuilding, construction, military, and farming [25]. A study based on a Canadian population (aged 30–100) found that long-term noise exposure increased the severity of presbycusis and prevalence of tinnitus [26]. Continuous exposure of 2-month-old C57BL/6J mice to noise resulted in increased auditory thresholds at 6 months of age, morphological damage to the spiral ganglion neurons (SGNs) of the cochlea, and a reduction in the number of banded synapses in the inner hair cells [27].

Some ototoxic medications are potentially associated with the incidence of presbycusis and disease progression. A population-based longitudinal study showed that older adult participants taking loop diuretics or nonsteroidal anti-inflammatory drugs had an increased risk and severity of hearing loss over a 10-year period [28]. It has also been shown that hearing loss in Fischer 344/NHsd rats exposed to cisplatin worsens with age [29]. In addition, there are potentially ototoxic chemicals in some workplaces, such as occupational exposure to organic solvents or metallic elements, which can lead to varying degrees of hearing loss [30]. A study of 1117 workers exposed to solvents (xylene, styrene, a mixture of n-hexane and toluene) alone or in combination with noise found that exposure to organic agents exacerbated noise-induced hearing loss and that co-exposure to both greatly increased the incidence of hearing loss [31]. An experiment exposing rats to noise or styrene found that noise and SGNs might aggravate presbycusis [32]. Manganese, a neurotoxic element associated with age-related diseases, was found to accelerate presbycusis in young adult mice in studies in which it mediated ototoxicity, a mechanism of action associated with neurodegenerative lesions in mouse SGNs caused by impaired c-Ret [33].

3.3. Lifestyle factors for presbycusis

Lifestyle is also a major factor that influences presbycusis. Healthy dietary patterns can help reduce the risk of hearing loss [34]. However, bad food habits, such as the consumption of high-sugar or fatty foods, smoking, and alcohol abuse, may drive the progression of presbycusis. Compared with non-smokers or former smokers, hearing loss in smokers is further aggravated, and there is a need for tight control of low-density lipoprotein cholesterol [35]. A population-based cross-sectional analysis revealed that the dietary intake of cholesterol and monounsaturated fats may be considered as potential risk factors for hearing loss among older adults [36]. High-fat dietary intake is one of the main triggers of atherosclerosis, and poorer hearing may be due to lower cochlear blood flow in elderly patients with carotid atherosclerosis which was speculated in a cross-sectional cohort study [37]. A prospective cohort study in southern Italy observed that sugar-rich beverages (fruit juices) increased serum triglyceride levels, which may affect hearing function

[38]. In a study on the association between presbycusis and nutrition, a higher intake of riboflavin, niacin, and retinol in 4742 participants was negatively correlated with the prevalence of presbycusis [39]. Smoking may aggravate presbycusis in patients with diabetes [40]. Therefore, healthy eating habits, such as reduced sugar and oil consumption, should be maintained, and malpractices, such as smoking and alcohol consumption, should be reduced to reduce the incidence of presbycusis.

3.4. Molecular mechanisms and related pathways of generation and progression for presbycusis

During the pathological process of presbycusis, cochlear dysfunction includes sensory cell loss, atrophy of the stria vascularis, and loss of the SGNs, with associated mechanisms involving oxidative stress, mitochondrial dysfunction and inflammation [41].

3.4.1. Correlation of oxidative stress and mitochondrial dysfunction with presbycusis

Oxidative stress is thought to be an important contributor to aging. Nicotinamide adenine dinucleotide phosphate (NADPH) is an important cofactor in the antioxidant system. NADPH oxidase (NOX) acts as an important source of ROS, and NOX activation can lead to presbycusis, whereas deficiency of the NOX subunit $p22^{phox}$ prevents age-related lesions of the auditory system [42].

ROS are one of the stressors induced by nuclear factor-E2-related factor 2 (Nrf2), a key transcription factor that mediates the oxidative stress signaling pathway and plays a critical role in maintaining redox homeostasis and preventing oxidative damage (Fig. 2). Nrf2 has been reported to be localized mainly in the inner and outer hair cells and supporting cells of the organ of Corti, as well as in the vestibular sensory epithelium. Nrf2 immunoreactivity is reduced in the cochlear tissue of older individuals [43]. During presbycusis progression, Nrf2 exerts a protective effect by upregulating the expression of antioxidant enzymes. The number of hair and spiral ganglion cells of Nrf2 knockout mice is significantly reduced compared to that in wild-type mice with age [44]. A study based on a candidate gene approach showed that increased levels of oxidative stress, accompanied by insufficient Cx26 expression and dysregulation of the Nrf2/ARE pathway in the cochlea, are the causes of presbycusis [45]. The Keap1-Nrf2 system is a key defense mechanism for cellular and biological responses to redox abnormalities and contributes to the prevention and mitigation of physiological aging and age-related diseases [46]. At 12 months of age, Keap1 knockout mice had more intact cochlear tissue morphology at the apical and middle turns, higher expression levels of some Nrf2 target genes than WT mice, and reduced accumulation of oxidative stress markers (4-HNE and 8-OHdG), suggesting that Nrf2 activation caused by Keap1 knockout is the key to attenuating presbycusis [47]. It has been revealed that mtDNA damage, apoptosis, and degeneration are involved in the development of central presbycusis and that activation of Nrf2-mediated antioxidant signaling maintains mtDNA integrity and delays aging [48]. It has also been suggested that deuterated oxygen supplementation slows metabolism and reduces endogenous oxidative stress, as evidenced by the reduced activity of the Nrf2/HO-1/glutathione axis [49].

Mitochondria are the main source and site of ROS production, and their structure, properties, and functions are altered during aging [50]. Cochlear aging involves mitochondrial redox imbalance and mtDNA damage are involved in the cochlear aging process [51]. Increased mitochondrial reactive ROS levels promote cochlear cell senescence and contribute to the accelerated onset and development of presbycusis [52].

Isocitrate dehydrogenase (IDH) 2 plays a key role in protecting mitochondria from oxidative stress. Loss of IDH2 accelerated hearing loss in 24-month-old mice, exhibiting increased oxidative DNA damage with apoptosis, severe SGNs and hair cell loss, and decreased mitochondrial oxygen consumption in HEI-OC1 cells with IDH2 gene knockdown [53]. Furthermore, a decrease in nicotinamide adenine dinucleotide (NAD^+) levels during senescence leads to a cellular and mitochondrial decline [54]. Sirt3 activates oxidative metabolism by deacetylating several mitochondrial enzymes. CMP-Neu5Ac hydroxylase-null mice exhibit presbycusis, and the mechanism of action may be related to Sirt3 downregulation, which in turn regulates ROS-induced oxidative damage and

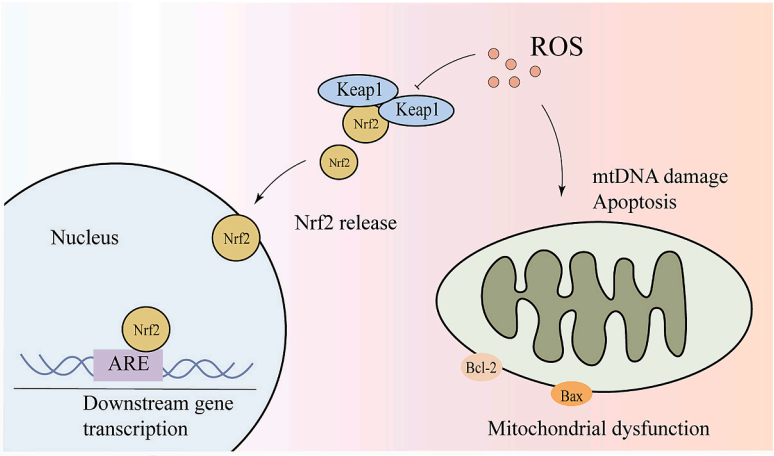

Fig. 2. Nrf2-mediated oxidative stress and mitochondrial dysfunction as part of the pathogenesis of presbycusis.

mitochondrial dysfunction [55].

3.4.2. Autophagy of progression for presbycusis

Research on the auditory system associated with aging has shown that mitochondrial damage caused by mtDNA deletion and increased ROS levels can be ameliorated by the autophagic pathway [56]. Autophagic dysfunction in the progression of aging has been extensively studied, particularly mitophagy (Fig. 3), which can maintain mitochondrial homeostasis by removing dysfunctional mitochondria from cells [57]. An imbalance between mitophagy and mitochondrial biogenesis can lead to oxidative stress and cochlear hair cell damage during aging. The marked loss of mitochondrial biogenesis and mitophagy in the cochlea with increasing age has emerged as a potential mechanism for age-related auditory system dysfunction [58,59]. Age-related defects in autophagy may lead to increased apoptosis of SGNs [60]. Relevant studies have shown that miR-34a expression is upregulated in the aging cochlea and that the activation of miR-34a inhibits ATG9A, impairs autophagic flux, and promotes cell death, whereas an appropriate increase in autophagy can reduce inner ear damage and prevent or delay presbycusis [61,62]. The PI3K/Akt/mTOR pathway is an important pathway that regulates cochlear autophagy in the inner ear and mediates cell aging [63]. It has also been shown that Sirt1 acts as an important regulator of autophagy in presbycusis, and its activation can exert a slowing effect on presbycusis by restoring autophagy [14].

3.4.3. Correlation of inflammation with presbycusis

Aging is also strongly associated with chronic low-grade inflammation, and the phenomenon of "chronic inflammation", which worsens with age, plays a key role in the pathogenesis of presbycusis [64] (Fig. 4). A cross-sectional analysis of a cohort study showed a significant correlation between inflammatory markers, such as white blood cell count, neutrophil count, interleukin-6, c-reactive protein levels, and hearing thresholds in elderly individuals [65]. Another cohort study showed that the signaling cascade of TNF-α was also associated with presbycusis [66]. Evidence of chronic inflammation has been found in aging cochlea, providing a new strategy for preventing and treating presbycusis [64]. This inflammatory process is a phenomenon of immune senescence, and there is evidence that the transcription factor nuclear factor kappa-B (NF-κB) is upregulated in aging cochlea, and that the NF-κB interacting molecules TNF-α and prostaglandin-endoperoxide synthase 2 are also expressed in the spiral ligaments and vascular striae of the lateral wall, suggesting that inflammation and immune responses are regulated in the aging process of cochlear in presbycusis mice [67]. Activated levels of caspase-1, Interleukin-1β, Interleukin-18 and nucleotide-binding structural domain-like receptor protein 3 (NLRP3) were elevated in the inner ear of aged mice compared to young mice; activation of NLRP3 contributes to the assembly of inflammatory vesicles and facilitates subsequent inflammatory events in the cochlea of aging mice [68].

Presbycusis is associated with increased oxidative stress, inflammation, and autophagic stress. SAMP8 mice show a range of premature manifestations characterized by oxidative damage, chronic inflammation, and reduced mitochondrial complex activity, which are similar to the changes observed in human presbycusis [69]. Overexpression of glucose-6-phosphate dehydrogenase triggers hypo-inflammation and acts as a positive regulator of the inflammatory response, thereby protecting the cochlea from ROS-derived oxidative damage [70]. Deficiency of insulin-like growth factor, which causes presbycusis, controls inflammation and oxidative stress, and plays a potential role in presbycusis-related mechanisms [71].

The above literature shows that the pathological mechanisms underlying presbycusis are complex and heterogeneous. Oxidative stress is present throughout the pathology of presbycusis and can occur in conjunction with mitochondrial dysfunction, abnormal autophagy, and inflammation. Crosstalk between mechanisms such as ROS-induced mtDNA damage and inflammation due to oxidative damage is also important in presbycusis.

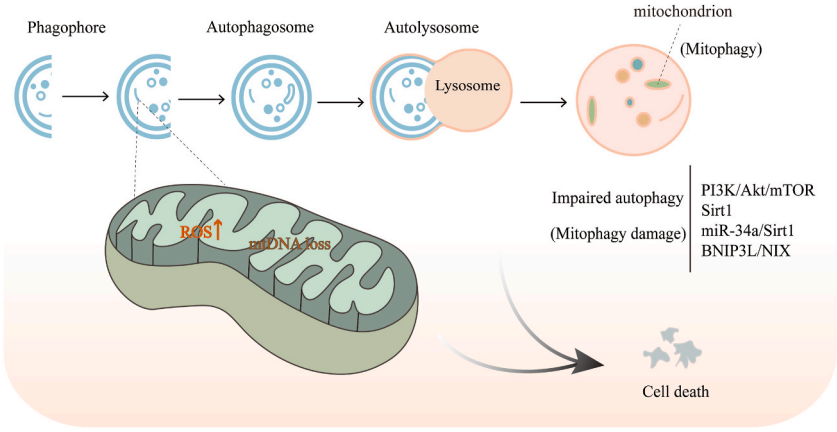

Fig. 3. Impaired autophagy (mitochondrial autophagy) in the pathological process of presbycusis, associated with increased ROS and mtDNA deletion.

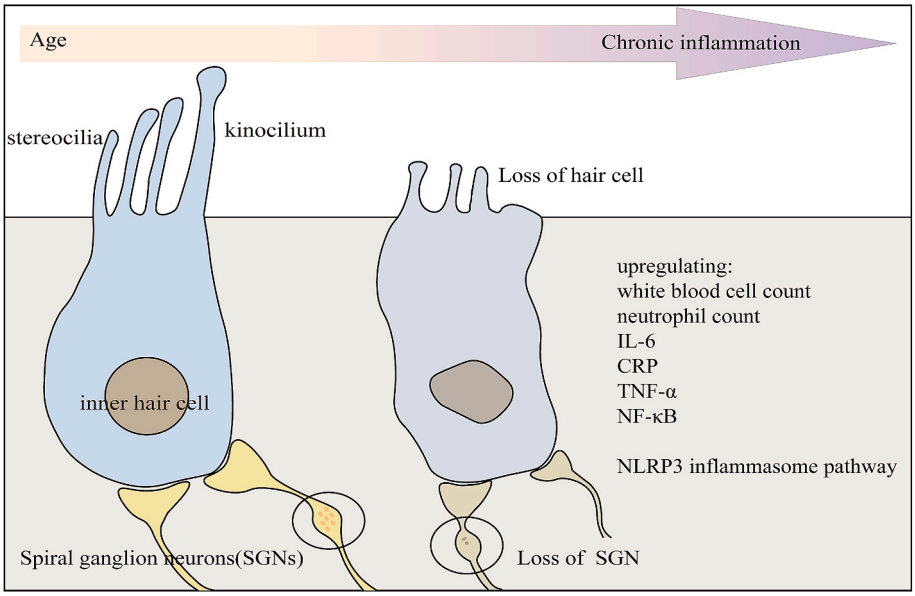

Fig. 4. Increased loss of cochlear inner ear hair cells and SGNs with advancing age.

4. Research progress in therapeutic approaches for presbycusis

Presently, hearing aids [72–74], and cochlear implants [75–77] are effective means of improving hearing and quality of life in older people. However, only a small proportion of people continue using hearing aids, mainly due to its economic burden, issues with comfort, equipment maintenance and social stigma [78,79]. Similarly, the high cost of cochlear implants severely limits their affordability, with market penetration rates of approximately 20 % in developed countries and less than 1 % in developing countries [80]. In addition, there are clinical trials evaluating the ameliorative effects of water-soluble coenzyme Q10 formulation on presbycusis [81,82]. Animal studies have shown that istradefylline, a small molecule antagonist of adenosine A2A receptor, improved cochlear hair cell survival in C57BL/6J mice [83]. The combination of antioxidants effectively lowered the auditory brainstem response (ABR) threshold in presbycusis mice [84]. Lecithin improves age-related hearing loss by protecting mitochondrial function in the rat cochlea [85]. However, there are no specific drugs available for the treatment of presbycusis.

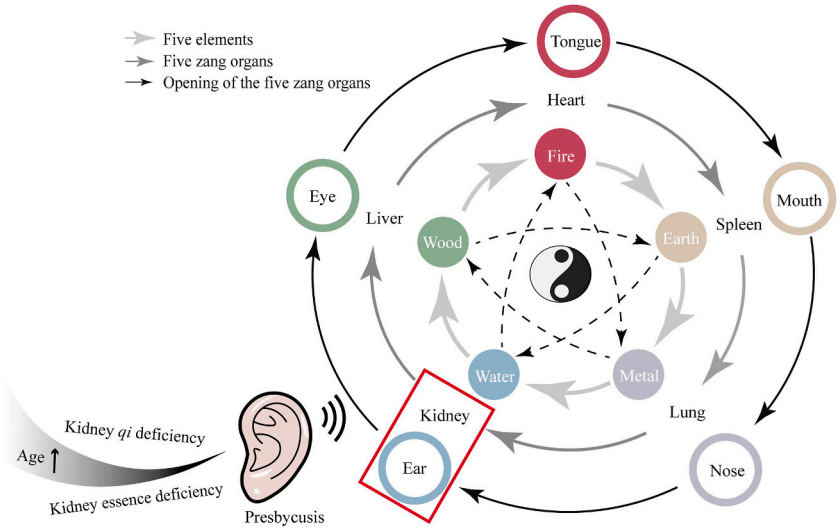

Fig. 5. A schematic diagram of the development of presbycusis based on the fundamentals of TCM: the Kidney stores essence and opens into the ears. Deficiency of kidney *qi* and essence with increasing age is one of the causes of presbycusis.

5. TCM possibilities for prevention and treatment of presbycusis

TCM has been used in Chinese culture and history for millennia [86], and the basic theories and treatments of TCM are used throughout the development of a wide range of diseases. According to TCM, the kidney store essence. Kidney essence is the basic substance that maintains the activities of the human body and plays an important role in all life processes. The ears are the opening orifices of the kidney and are nourished by kidney essence and *qi* (*energy*) , which are associated with hearing sensitivity. If the kidney essence is full and well-nourished, the hearing will be sensitive, and the resolution will be high. In contrast, in kidney essence deficiency, the marrow lacks nourishment, resulting in hearing loss and tinnitus.

With an increase in age, kidney *qi* and essence are gradually insufficient, leading to malnourishment of the ears and subsequently, hearing loss. Consequently, kidney essence failing to nourish the ears contributes to presbycusis (Fig. 5). According to one study, the correlation between presbycusis and kidney deficiency in TCM from a metabolic perspective was positively correlated with the score of

Table 1
Prevention and treatment of presbycusis with TCM.

Approach	Experiment evidence	Name	Objects (Gender; Age; Intervention)	Mechanism	Refs
Formula	*In vivo*	Erlong Zuoci Decoction	C57BL/6J mice; Male, 3 m; fed	anti-apoptotic (mRNA and protein of p53, Bak↓)	[88]
		Erlong Zuoci Pill	GM-induced cochlear basilar membrane of kunming mice (P2–P3)	Reduction of GM-induced ototoxicity (cochlear hair cells loss ↓)	[89]
		Zuogui Pill	Dgal-induced C57BL/6 mice; Male; fed	hearing threshold levels of 8 kHz and 16 kHz ↓	[90]
		Jian Er preparation	C57BL/6J mice; half male and female; drinking tap water containing TCM	Anti-oxidant (ABR thresholds from 8 to 48 KHz ↓, MDA contents in cochlear tissue, auditory cortex and liver ↓)	[91]
		Jian Er preparation	C57BL/6J mice; half male and female; drinking tap water containing TCM	Anti-oxidation, anti-apoptotic (lipid peroxidation and MDA levels, Cyt-C and caspase-3 mRNA expression ↓)	[92]
		Fucong Decoction	DBA/2J mice; half male and female; 4w; orally	Prevent the process of hair cell death (ABR threshold ↓, survival rate of cochlea hair cells↑; protein of prestin↑)	[93]
	In vitro	Erlong Zuoci	H_2O_2-induced HEI-OC1 cell	Anti-aging, anti-inflammatory (SA-β-gal activity ↓, proteins of p-P53, P21 and p-Stat3 ↓, *p*-ERK↑)	[94]
		Erlong Zuoci Pill	HEI-OC1 cell transfected with a miR-34a mimic	Regulate autophagy and apoptosis (protein of miR-34a, ac-p53, cleaved caspase 3, LC3II and p62↓, SIRT1↑)	[95]
		Yiqi congming Decoction	HEI-OC1 cells	Modulate apoptosis (ΔΨM↑, γH2AX↓, cleaved caspase-3↓)	[96]
Extract	*In vivo*	KRG	C57BL/6 mice; Male; 3 m; drinking water containing KRG	Modulate mitochondrial apoptotic (Bcl-xL↑, Cyt-C↓)	[97]
		Ginkgo biloba extract (EGb761)	SD rat; Male and female; 12 m; drinking water contain EGb761	Anti-oxidation, anti-apoptotic (ATP ↑, protein of Bax, caspase-3/7 and caspase 9↓, Bcl-xL ↑)	[98]
		Polyphenols	SD rat; 3, 6, 12, 18 24 m; female; mixture of polyphenols in the drinking water	Anti-oxidation (improved ASSR and tone-burst ABR auditory thresholds; ROS, RNS, superoxide anions and nitrotyrosine↓; caspase-3, caspase-9, annexin-V, p53, 8-OHdG and Bax↓, Bcl-2, ATP↑)	[99–101]
Compounds		Resveratrol (PubChem CID: 445154)	C57BL/6 mice; 1–3 m, 12–16 m; dietary supplementation with Resveratrol	ABR threshold shifts at 4, 8 and 16 kHz↓, loss of outer hair cells in the apical turn↓	[102]
		Apocynin (PubChem CID: 2214)	D-gal induced SD rat; Male; 1 m; intraperitoneally administered	Anti-apoptotic (protein of 8-OHdG, p-p47phox, TNFα, UCP2, Cyt-C and cleaved-caspase 3↓, activity of NADPH, H_2O_2↓, T-SOD and GSH-Px ↑, levels of ATP and MMP ↑)	[103]
	In vitro	Ursolic Acid (PubChem CID: 64945)	H_2O_2-induced HEI-OC1 cell	Anti-oxidation (activity of MDA↓, CAT and GPX↑)	[104]
		Resveratrol (PubChem CID: 445154)	H_2O_2-induced HEI-OC1 cell	Anti-apoptotic (Ac-p53↓, 4HNE↓, 5-fluorouracil↓, miR-34a↓)	[102]
Acupuncture	Clinic		126 senile SNHL patients; 60–69 years old; Acupuncture points: Tinggong (SI 19), Tinghui (GB 2), and Yifeng (SJ 17), acupoint injection and auricular point pressing	Improve pure tone hearing threshold and tinnitus	[105]

↑, upgrade; ↓, downgrade.

kidney deficiency in TCM, which may be associated with glutathione metabolism, amino acid metabolism, glucose metabolism, N-methyl-D-aspartic acid receptor (NMDA) receptors, γ-aminobutyric acid (GABA) receptors, and other related material bases [87].

5.1. The action of Chinese medicine formulas and specific application

Chinese medicine formulas interventions for the treatment of presbycusis have been confirmed in several experiments *in vitro* and *in vivo* with different mechanisms in TCM (Table 1.).

5.1.1. The action of tonify the kidney

The view that presbycusis should be treated from a "Kidney" perspective has been taken seriously by many scholars. The Erlong Zuoci (ELZC) formula is commonly used in TCM clinics to treat hearing loss due to kidney deficiency and consists of Liu Wei Di Huang (LWDH) plus Radix Bupleuri and Magnetitum. A classical kidney tonic formula, LWDH improves or cures aging-related diseases [106]. In presbycusis mice, ELZC could lower hearing threshold levels and reduce SGN damage, and this mechanism of action may be related to the P53/Bak-mediated apoptosis pathway [88]. In *vitro* culture of newborn mouse cochlear spiracles revealed that ELZC had a protective effect against gentamicin-induced ototoxic damage, and that its disassembled formulation, LWDH, was a major formula in protecting cochlear hair cells [89]. Network pharmacological analysis showed that ELZC contains compounds with antioxidant and anti-inflammatory biological activities that cross-target biological processes, including cell proliferation, immune response, and inflammatory response, and may improve aging, inflammation, and synaptic connectivity in mouse auditory cells (HEI-OC1) through the c-Jun N-terminal kinase/signal transducer and activator of transcription 3 and extracellular regulated protein kinases cascade signaling pathways [94]. In age-induced SNHL, autophagic activity decreases with increasing age, and upregulation of autophagy promotes the survival of senescent inner ear hair cells and slows the degeneration of auditory cells [107]. miR-34a overexpression caused HEI-OC1 auditory cell death and autophagosome accumulation, and ELZC pills regulated autophagy through the SIRT1/p53 signaling pathway to inhibit apoptosis, thus exerting otoprotective effect [95].

Additionally, another classic formula to tonify kidney essence is called Zuo Gui Pill, which is modified from LWDH, also attenuates cognitive decline with the effect of protecting against D-galactose-induced hearing impairment [90].

5.1.2. The action of circulate blood

The Chinese herbal formula Jian Er, which tonifies the kidney and strengthens the spleen to circulates blood and opens the orifices, significantly improves hearing thresholds, and reduces malondialdehyde content in the cochlea and auditory cortex of presbycusis

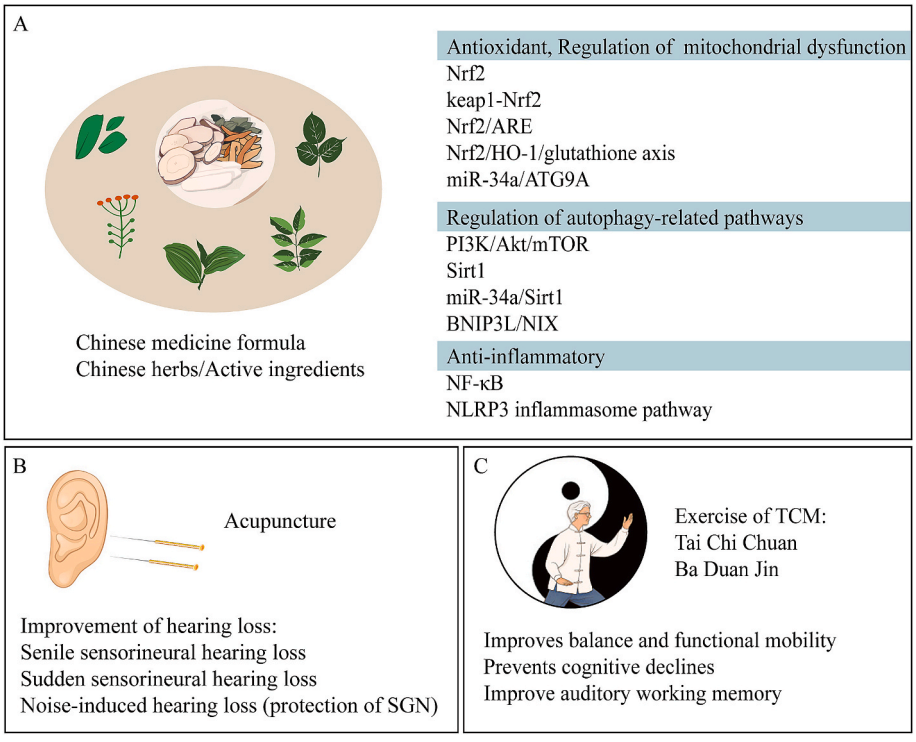

Fig. 6. TCM intervention in presbycusis. (A) TCM compound/herbs and their active ingredients can intervene in presbycusis by exerting antioxidant, autophagy-regulating and anti-inflammatory effects. (B) Acupuncture has an improving effect on hearing loss by stimulating acupuncture points. (C) Tai Chi Chuan or Ba Duan Jin can improve balance and functional mobility as well as improve auditory working memory.

model mice, which is related to the antioxidant effect of the formula [91]. Further studies showed that it also reduced the number of cochlear basement membrane hair cells with SGNs damage and inhibited caspase-mediated mitochondrial apoptotic pathways in the same model mouse [92]. Fucong Decoction could activate blood to resolve stasis. In animal experiment, it effectively prevented and delayed the development of presbycusis by upregulating prestin to improve the survival of mouse cochlear hair cells [93].

5.1.3. The action of tonify qi of the spleen and stomach to ascend yang

Yi-Qi Cong-Ming decoction, which tonifies *qi* of the spleen and stomach to ascend yang, exerted a protective effect against presbycusis by alleviating oxidative stress-induced auditory hair cell death by regulating DNA damage and apoptosis [96].

The results from the above-mentioned studies show that most herbal formulations have been studied *in vivo* and *in vitro*, and the specific mechanisms of effective intervention in presbycusis mainly include regulation of oxidative damage, autophagy and apoptosis (Table 1.) (Fig. 6 A). However, Chinese medicine formulas are composed of a variety of Chinese herbs in strict compliance with the principles of formulas and contain complex chemical components with multi-level and multi-targeted pharmacological effects, and the quality control of the formulas is yet to be optimized. Therefore, the study of the pharmacology of herbal compound prescriptions needs to be encouraged.

5.2. The mechanisms of Chinese herbs and active ingredients

In addition to Chinese medicine formulas, some traditional oriental herbs and their active ingredients have shown beneficial effects in the treatment of presbycusis (Table 1.).

5.2.1. Ginsenosides

Ginsenosides are the main active constituents of ginseng. One study found that red ginseng delayed early onset hearing loss and progressive vestibular dysfunction in C57BL/6 mice with increasing age, partly by regulating the mitochondrial apoptotic pathway [97].

5.2.2. Ginkgo biloba extract

Similarly, the antioxidant properties of Ginkgo biloba extract are widely used in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [108]. Ginkgo biloba leaf extract EGb761 exerts beneficial effects on presbycusis by increasing ATP levels and downregulating the expression of pro-apoptotic proteins (Caspase-3, Caspase-7) in the aging rat cochlea [98].

5.2.3. Polyphenols

Polyphenols are important natural products that are widely found in herbal medicines such as Veratrum grandiflorum and curcuminoids [109]. It has been shown that a mixture of polyphenols (tannic acid, resveratrol, quercitine, rutin, gallic acid and morin) can significantly improve the auditory steady state response and tone-burst ABR auditory thresholds in rats [99]. It was further observed that the levels of ROS and reactive nitrogen species in the rat cochlea increased with age and decreased after polyphenol treatment, and that SOD and GPx enzyme activities were restored [100]. The polyphenol mixture also inhibited age-related apoptotic signaling by reducing oxidative stress in the rat cochlea, which was mainly associated with the blockade of pro-apoptotic Bax and p53 and the activation of anti-apoptotic Bcl2 [101].

5.2.4. Ursolic acid

Cornus officinalis also attenuates inner ear dysfunction, and ursolic acid (PubChem CID: 64945), its main active ingredient, has a protective effect against H_2O_2-induced HEI-OC1 cell damage, which is associated with the inhibition of lipid peroxidation and modulation of the activities of antioxidant enzymes catalase (CAT) and glutathione peroxidase (GSH-Px) [104].

5.2.5. Resveratrol

Resveratrol (PubChem CID: 445154) is a potent compound found in many foods and oriental herbs. It acts as a Sirt1 activator, protects against miR-34a overexpression-induced HEI-OC1 cell death, and reduces hearing threshold changes and hair cell loss in C57BL/6 mice, which is largely dependent on the miR-34a/SIRT1/p53-mediated apoptotic pathway [102].

5.2.6. Apocynin

Apocynin (PubChem CID: 2214) has been reported as a nitrogen oxides (NOX) inhibitor present in the leaves of *Apocynum venetum* [110], and is an active component of *Picrorrhiza kurroa* [111]. In D-gal-induced rats, the snail ventral nucleus (VCN) exhibited oxidative damage, mitochondrial dysfunction, and apoptosis. Apocynin (PubChem CID: 2214) attenuated NOX-related oxidative stress and mitochondrial DNA damage by inhibiting NOX activity, H_2O_2 levels, DNA damage biomarker 8-OHdG expression, and mtDNA deletion in the VCN, and increasing total superoxide dismutase and GSH-Px activity, thereby partially blocking caspase-3-dependent apoptosis and effectively preventing or delaying the development of central presbycusis [103].

The above studies suggest that single herbs and their active ingredients have considerable potential for the prevention and treatment of presbycusis, with relevant mechanisms focusing on antioxidant and anti-apoptotic effects (Table 1.) (Fig. 6 A).

5.3. The application of acupuncture

Acupuncture, a traditional Chinese treatment method, can be used to prevent or treat various diseases, such as neurological and metabolic disorders, by stimulating the relevant acupuncture points on the body surface through needle insertion and rotation [112]. According to case reports, patients with hearing loss showed significant improvements in hearing after receiving acupuncture treatment [113,114]. Clinical studies have shown that the combination of acupuncture and medical therapy is effective in treating sudden deafness. A randomized controlled trial observed differences in the efficacy of the three approaches for the treatment of senile SNHL and found that combined treatment was superior to acupuncture and oral mecobalamin alone [105]. Another clinical trial showed that a combination of acupuncture and Western medicine combined therapy (WMCT) was a more effective intervention for sudden SNHL than WMCT alone [115]. In addition to the clinical trials mentioned above, an experimental animal study found that electro-acupuncture intervention could promote hearing recovery after noise exposure by increasing SGN density.

The above study shows that acupuncture treatment for presbycusis is less commonly reported than for sudden deafness (Table 1.) (Fig. 6 B). On the one hand, it may be that acupuncture may be less effective in chronic conditions (age-related degenerative lesions) than in acute lesions. On the other hand, given the body constitution of the older adults and the complex pathogenesis, the variable efficacy is closely related to the absence of complete treatment rules based on basic principles, as well as different treatment cycles.

5.4. Exercise of TCM: Tai chi Chuan, Ba Duan Jin

Clinical studies have revealed that group audiological rehabilitation, exercise intervention, and social contact can improve presbycusis and associated isolation it brings [116]. Popular traditional Chinese mind-body exercises including Tai Chi Chuan and Ba Duan Jin practices can improve balance and enhance the quality of life in older adults [117,118]. In a study on the rehabilitation of children with congenital SNHL, Tai Chi Chuan and conventional exercise training improved balance and functional mobility [119]. Moreover, numerous clinical studies have confirmed that Tai Chi Chuan and/or Ba Duan Jin are effective exercises for preventing cognitive decline in the elderly [120–122]. Due to the higher risk of falls in people with presbycusis, sequential cognitive and exercise training improves auditory working memory [123].

There are no reports of traditional exercise in presbycusis. However, it has become influential in age-related diseases. The positive physical and psychological effects of these traditional exercise methods have been validated in clinical trials (Fig. 6 C), thereby promoting physical and mental health and enhancing the overall physical fitness of the elderly population.

6. Conclusions, implications and future perspectives

6.1. The conclusion of the review

We have reviewed the pathogenetic factors associated with presbycusis, related to genetic factors, environment, lifestyle, and molecular mechanisms related to oxidative stress, mitochondrial dysfunction, and inflammatory pathways. Traditional Chinese medicine interventions could offer opportunities in the prevention and treatment of presbycusis using active ingredients of herbs or formulas, acupuncture, and exercise such as Tai Chi Chuan or Ba Duan Jin. Fig. 7 illustrates the overview of the article.

Given the intricate pathogenesis of presbycusis, Chinese medicine may focus on a variety of pathways and targets to coordinate the disease's progression from various angles. This could contribute to the disease's pathological progression in a variety of ways and offer a fresh perspective on presbycusis intervention and treatment. This article searched for the effects of Chinese herbal compounds or

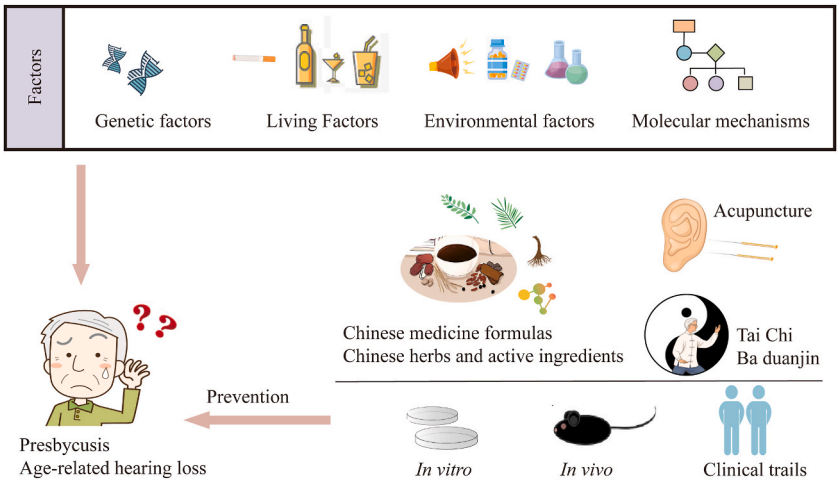

Fig. 7. The overview of the article.

herbs and their active ingredients on oxidative stress and its resulting mtDNA damage, mitochondrial dysfunction, relevant targets or pathways including Nrf2, keap1-Nrf2, Nrf2/ARE, Nrf2/HO-1/glutathione axis, autophagy-related pathways such as miR-34a/ATG9A, PI3K/Akt/mTOR, Sirt1, BNIP3L/NIX, miR-34a/Sirt1, and the inflammation-related NF-κB, NLRP3 inflammatory vesicle pathway. By acting synergistically on multiple targets and pathways, TCM can maintain the redox status, regulate mitochondrial function, modulate autophagy, reduce inflammation, and ultimately improve presbycusis.

Although the role of acupuncture in presbycusis has rarely been reported, it is commonly used to treat age-related diseases. In TCM theory, most elderly people are believed to have deficiency of heathy qi (weak immune system in modern medicine), acupuncture can be used as a method to reinforce or tonify the body based on individualized pattern identification. With advances in biotechnology, the mechanism of action of acupuncture needs to be further elucidated. In clinical practice, the effectiveness of acupuncture is closely related to the acupuncture points, needling technique, treatment period, and individualized body constitution. Therefore, more basic research and clinical trials are needed at a later stage to establish and improve standardized acupuncture treatment protocols, thereby providing evidence for the potential mechanisms of action of acupuncture in the treatment of presbycusis.

Traditional exercise methods are beneficial for rehabilitation and healthcare. As classic examples of the "integration of martial arts and medicine", Tai Chi Chuan and Ba Duan Jin act to balance between yin and yang, maintain the free flow of qi within meridians and collaterals. They are characterized by movements (upper-lower coordination, opening, and closing) of the limbs, twisting and turning, flexion and extension, blowing and breathing (opening with breathing out and closing with breathing in, opening with breathing in and closing with breathing out), to achieve the purpose of strengthening the body.

6.2. The strengths and limitations of the review

The retrieval approach might not be sufficient because the database only contains information in English and Chinese. The majority of research on the prevention and treatment of presbycusis with TCM now comes from *in vivo* and *in vitro* studies, which have limits for examining the formula effects of presbycusis. Additionally, the molecular pathways behind the therapeutic benefits of this prescription are yet unknown. In order to completely identify the possible targets and pertinent signaling pathways involved, more investigation using standardized and rigorous clinical trials is therefore required in order to uncover the underlying process.

6.3. The implications and future perspectives of the review

Presbycusis, an age-related chronic illness, has a substantial influence on social and public health due to the tendency of an aging population. First and foremost, we should protect our ears by living a healthy lifestyle that includes avoiding loud noises, using ototoxic medications and chemicals, quitting smoking, drinking alcohol, and using nutritional supplements (vitamins) whenever feasible. Second, effective intervention strategies for hearing loss in elderly people need to be further explored through a thorough, individualized assessment, as the pathophysiological mechanisms involved in presbycusis have not yet been fully elucidated, combined with the complex and varied clinical presentations of presbycusis.

The Chinese medicine prescription is made up of a wide variety of traditional Chinese herbs, and the total thing comprises different substances that work together to regulate the body. On the one hand, holistic approach of TCM is one of the fundamental qualities; it not only aids in the treatment of illnesses but also functions as conditioning and has fewer negative effects. TCM, on the other hand, is advantageous for illness prevention and has a positive impact on sustaining health. Additionally, the cost of modern therapies, such as the choice of hearing aids and cochlear implants, is a significant burden for less fortunate households or developing countries. Acupuncture and exercises such as Tai Chi Chuan or Ba Duan Jin present an economical approach to prevent and treat presbycusis among the elderly population.

Presbycusis needs more attention as the population ages more rapidly. In order to lessen the negative impacts of presbycusis on the elderly's quality of life, cognitive function, mood, behavior, and social activities, TCM has certain benefits in its treatments and prevention.

Funding statement

This work was supported by grants from Shanghai Municipal Commission of Health and Family Planning, NO. ZY (2021–2023)-0208, NO. 202340284 and the National Natural Science Foundation of China (81774020).

Institutional review Board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

No data was used for the review described in the article.

CRediT authorship contribution statement

Li Yan: Writing - original draft, Methodology, Data curation. **Yan Huo:** Writing - original draft, Methodology, Data curation. **Jianrong Shi:** Supervision, Project administration, Funding acquisition, Conceptualization. **Yang Dong:** Writing - review & editing, Methodology, Conceptualization. **Hongsheng Tan:** Writing - review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank anonymous reviewers for the helpful comments. We would like to thank Editage [https://www.editage.cn/] for editing and reviewing this manuscript for the English language.

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