# Observation of the clinical efficacy of the treatment of otic neuralgica by dispelling wind and clearing heat,network pharmacological analysis and molecular docking

**Liang Xiangnan[1], Wu Huange[2]，He Jian[1]**

[1]The Third Affiliated Hospital of Naval Medical University, Shanghai 200000, China

[2]Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Jilin City, 110033, China

Introduction. Due to the acceleration of the pace of life, many interferences of external factors, the prevalence of otic neuralgia is increasing day by day.The disease has the characteristics of rapid onset, severe pain, recurrent attacks,which seriously affect the emotional state, life and sleep quality of patients,the routine use of non-steroidal anti-inflammatory drugs, anti-epileptic drugs in the treatment of the treatment, the course of treatment is poor, there will be many adverse reactions, such as allergies, gastrointestinal, liver and kidney function damage to different degrees. It is a safe and effective method to treat both symptoms and root causes with oral traditional Chinese medicine decoction, which is not easy to recur and has fewer adverse reactions.
Keywords. dispelling wind and clearing heat, detoxifying;otic neuralgia;network pharmacology ;molecular docking.

## 1 INTRODUCTION

There are three types of otic nuralgia:1. Primary otalgia, also known as otogenic otoalgia, is caused by the stimulation and compression of local pain nerve endings by one's own ear disease. 2. Secondary otalgia: also known as radiation otalgia, earache caused by nerve reflexes caused by anatomically related adjacent organs or systemic diseases. 3. Neuropathic otalgia, caused by sensory neuropathy distributed to the ear. Neuralgia in the ear refers to a sudden, sharp, lightning-like, knife-like, electrocautery, or tear-like pain in the ear involving the head and face, or even the neck. The patient's expression is abnormally painful, often covering his face with his hands or rubbing his face violently, the pain lasts for a few seconds to a few minutes and then stops returning as usual, but it may soon recur, and the frequency of attacks increases as the disease progresses. It is mostly located next to the nose, lips, gums and tongue on the affected side, and will also affect the deep ear, a small number of patients only have deep ear pain, and severe cases are often accompanied by reflex twitching of the facial muscles, and the corners of the mouth are pulled to one side. The etiology is not clearly reported, but it is mostly caused by infectious diseases such as herpes zoster virus infection, upper respiratory tract infection, and influenza; Tumors, trauma, metabolic diseases, vitamin B deficiency, excessive alcohol intake and intoxication, excessive exposure to toxic metals, vascular disease and other factors are related, mostly induced by touching, chewing, talking, brushing teeth, fatigue and other stimuli such as touching. It is mostly seen in the elderly, people with high blood pressure, diabetes, and autoimmune diseases.

## 2 MATERIALS AND METHODS

2.1 Subjects: A total of 30 patients who received outpatient treatment in our hospital were randomly divided into 2 groups.

2.1.1 Inclusion Criteria: The head CT, inner ear CT, and contrast-enhanced CT showed no space-occupying lesions or other abnormalities. Electronic ear endoscopy: bilateral external auditory canals are unobstructed,

no desquamation and redness, no pus, no invagination of both tympanic membranes, no perforation and pus, no turbidity and flushing, and clear anatomical landmarks. No nasal cavity or nasopharyngeal mass.

2.1.2 Exclusion Criteria: Migraine, trigeminal neuralgia, herpes zoster infection or post-encomic neuralgia, glossopharyngeal neuralgia, occipital neuralgia, otogenic otalgia, secondary otalgia.

2.2 Methods :They were randomly divided into treatment group and control group. The control group was given oral carbamazepine tablets 0.1g, 3 times/day; Ginkgo biloba extract tablets, 80mg, 3 times/day. The treatment group was given the following oral formula: Rehmannia 15g,Honeysuckle 20g, Forsythia 20g, vinegar Rhizoma Corydalis 20g, Angelica dahurica 10g, Salvia miltiorrhiza 15g, Scutellaria baicalensis 15g, Wild chrysanthemum 15g, Stir-fried fructus viticis 15g, Fried atractylodes 15g, Stir-fried burdock seeds 20g, Chinese violet 15g,Dandelion 15g, Tuckahoe 15g,Folium isatidis 20g（Isatis root 15g）,3 times/day; Ginkgo biloba extract tablets, 80mg, 3 times/day. Before treatment, the pain VAS score, the frequency and duration of attacks were scored by the four-point method, and the sleep quality score PSQI were performed for 1 week and 3 weeks, respectively.

2.3 Evaluation Criteria:

2.3.1 The National Institutes of Health developed the Visual Analogue VAS Score for Clinical Pain Measurement: Pain Level Scoring Criteria [1], Draw a 10cm straight line from left to right, a total of 10 points, 0 points are painless, 2 points are 1-3cm mild pain, 4 points are 4-6cm moderate pain, 6 points are 7-10cm severe pain, pain duration 0-2h is worth 1 point, 3h-6h is worth 2 points, 7h-24h is worth 3 points.

2.3.2 Frequency and duration of attacks: 0 minutes (painless), 1 minute mild pain (interval ≥7h, duration < 30s), 2 minutes moderate pain (interval 3h-6h, duration 30s-1min), 3 minutes severe pain (interval ≤2h, duration > 1min).

2.3.3 Sleep quality score PSQI: The Pittsburgh Sleep Quality Index was used to evaluate the sleep quality of patients. The scale consisted of two parts (19 items of self-assessment and 5 items of other assessment). The subjects were required to complete the questions and answers within 5 to 10 minutes, and the total score was within 0 to 20 points, which was inversely proportional to the degree of sleep quality.

2.4 Statistical Methods:

SPSS 26.0 statistical software was used to process the data, The counting data were represented by percentage first, the measurement data were represented by the mean（$\bar{x}\pm SD$） through $X^2$ test, and then the differences in the analysis of variance group were repeatedly measured by single factor. If the differences had statistical significance, $P<0.05$.

2.5 Network pharmacology analysis and molecular docking

2.5.1 Network pharmacology analysis

2.5.1.1 Screening and target prediction of the active ingredients of the drug of Shufeng Qingre Formula

Entered TCMSP, a pharmacology database and analysis platform of the TCM system (https://old.tcmsp-e.com/index.php),The active ingredients in Shufeng Qingre prescription were selected under the conditions of biological oral availability OB≥ 30% and drug-like properties DL≥0.18. The MW of the active ingredient through the above screening criteria is consistent with the MW in the Pubchem database (https://pubchem.ncbi.nlm.nih.gov) and retains its Canonical SMILES, If the MW of the same active ingredient in the two databases is different, the structure conversion is downloaded from the TCMSP platform to obtain Canonical SMILES. Canonical SMILES was screened into the SwissADME database (http://www.swissadme.ch) for active ingredients with a GI absorption score of "high" and a druglike-ness of at least 2 "yes".Eligible active ingredients were entered into the SwissTargetPrediction database and Probability>0.1 was selected as the screening condition to predict the corresponding target retention results.

2.5.1.2 Collection of gene targets for otic neuralgia

With“otic neuralgia”and “auricular neuralgia”as keywords,disease related targets can be searched through the Gene Cards database(https://www.genecards.org) and the OMIM database (https://omim.org)，and finally the intersection gene targets of the active ingredient and the disease target can be obtained.

2.5.1.3 Protein-protein interaction (PPI) network construction and screening of core targets for drug diseases

Enter the intersecting gene target into String(https://string-db.org) and download the desired result file. Cytoscape software v3.10.1 was used for further topological analysis, and the plug-in CytoNCA was selected to calculate the attribute values of each node, including between centrality (BC), degree centrality (DC) and closeness centrality (CC), and the core target genes were screened out according to the calculation results.

2.5.5.4 GO function and KEGG pathway enrichment analysis of core target genes

Input of core target genes into the David database (https://david.ncifcrf.gov), The functional annotation tool was selected for GO function analysis including biological process (BP), cell component (CC), molecular function (MF), and KEGG pathway enrichment analysis, and the screening condition was $P<0.05$. According to the Pvalue, a certain amount is selected to be visualized through micro-biosis (http://bioinformatics.com.cn/?keywords=pathway).

2.5.2 Molecular docking of active ingredients and target genes

Five active pharmaceutical ingredients with high values in the compound drug ingredient-disease-target-pathway network diagram were injected into the TCMSP platform to obtain the 2D structure of the small molecule.The core target in the PPI network diagram was selected to find the corresponding PDB, and the protein species Homo sapiens, resolution<3A, and protein sequence >270 were determined, and the protein was dehydrated and deligand by Pymol software. Proteins and small molecules were docked by Autodock software, stable objects were selected, and finally visualized with Pymol software.

## 3 CONCLUSION

3.1 The total effective rate of the control group was 60%, and the total effective rate of the experimental group was 85%, and the difference was statistically significant($P<0.05$)

3.2 Network pharmacological results

3.2.1 Screening and target prediction of the active ingredients of the drug of Shufeng Qingre Formula

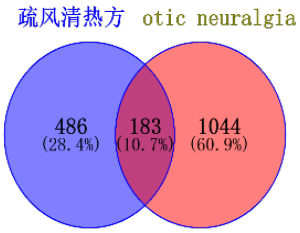
The absorbable active ingredients were 9 Honeysuckle, 13 Forsythia, 47 vinegar Rhizoma Corydalis, 15 Angelica dahurica, 2 Burdock seeds, 4 Wild chrysanthemum, 3 Atractylodes, 1 Tuckahoe, 21 Fructus viticis, 55 Salvia miltiorrhiza, 35 Scutellaria baicalensis and 4 Folium isatidis. The number of targets corresponding to the absorbable active ingredient was 669 after deduplication.

3.2.2 Collection of gene targets for otic neuralgia

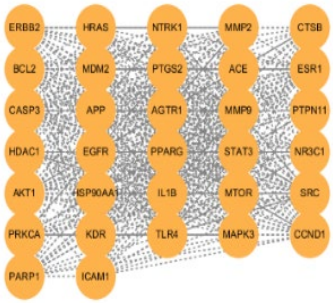
There were 1227 disease targets after deduplication, and 183 common targets were obtained by Venn diagram to treat disease and drug targets.

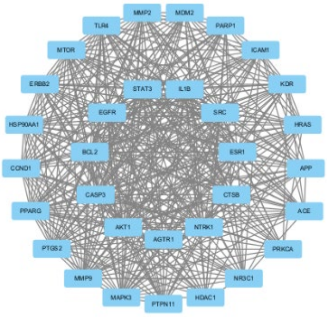
3.2.3 Protein interaction (PPI) network construction and core target screening

The common target was imported into Cytoscape software, and 183 nodes, 3413 edges, Betweenness unDir value was 167.4645, Closeness unDir value was 0.002919, and Degree unDir value was 37.30055. After screening under the above conditions, 32 nodes and 407 edges remained, and the number of core target genes was 32.




Compound and disease intersection genes

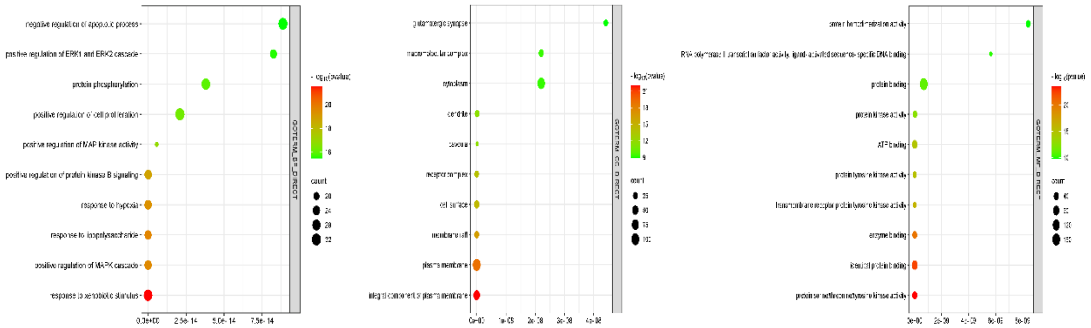


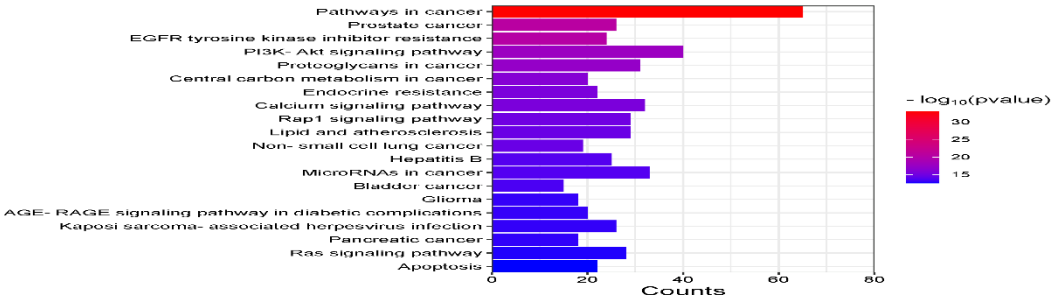



Compounds and core targets of disease

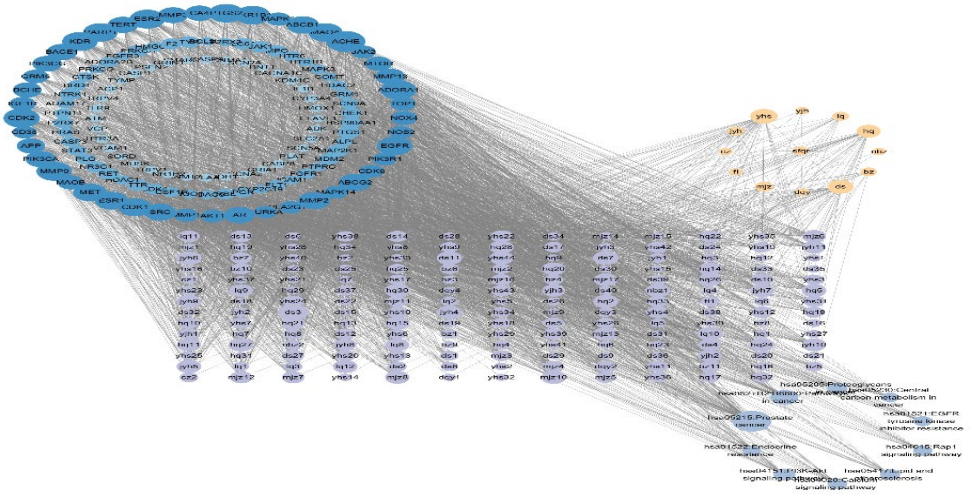
3.2.4 GO function and KEGG pathway enrichment analysis of core target genes

After GO enrichment analysis, 583 biological processes, 119 cell components and 90 molecular functions were collected. The top 10 digits were selected for visual analysis, as shown in the figure. Biological processes mainly include response to xenobiotic stimulus, positive regulation of MAPK cascade, positive regulation of ERK1 and ERK2 cascade, response to lipopolysaccharide, response to reaction, positive regulation of protein kinase B signal, positive regulation of MAP kinase activity, positive regulation of cell proliferation, protein phosphorylation, and negative regulation of apoptosis process. The cell components mainly include cell surface and cytoplasm, plasma membrane, membrane raft, receptor complex, caveola, dendritic and glutaminergic synapse. Molecular functions mainly include protein serine/threonine/tyrosine kinase activity, protein binding, enzyme binding, ATP binding, RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding, etc. After enrichment and screening of KEGG pathway, 160 pathways were obtained. The first 20 histograms showed apoptosis, RAS signaling pathway, pancreatic cancer, Kaposi's sarcoma-associated herpesvirus infection, AGE-RAGE signaling pathway in diabetic complications, glioma, bladder cancer, MicroRNA in cancer, Hepatitis B, Non-small cell lung cancer, lipid and atherosclerosis, Rap1 signaling pathway, Calcium signaling pathway, endocrine resistance, central carbon metabolism and proteoglycans in cancer, PI3K-Akt signaling pathway, EGFR tyrosine kinase inhibitor resistance may be important pathways for the treatment of otic neuralgia.






GO function and KEGG pathway enrichment map of core target genes

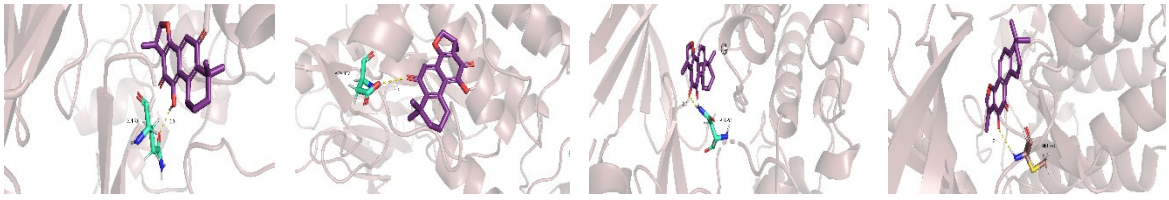


Drug-Active Ingredient-Disease Core Target-Pathway Diagram

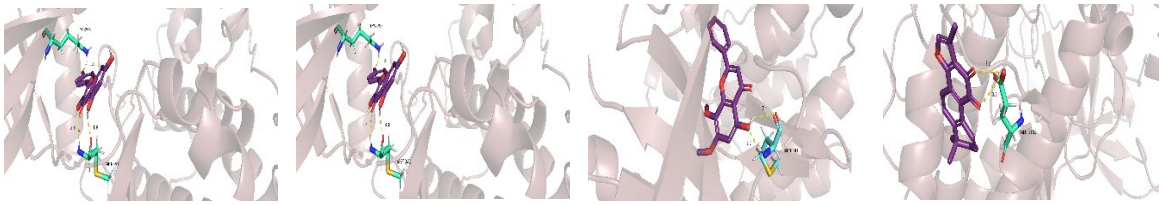
(The darker the color in the diagram, the greater the Degree value. The larger the circle, the greater the Degree value.)

## 3.3 Molecular docking results

Dehydrotanshinone II A（2651）,Moslosooflavone（8206）,Kaempferol（0422）,Miltionone II（7120）were selected as small molecules.AKT1（3o96）,KDR(6xvk) and SRC(2bdj) were used as proteins, and the binding results of both were less than -5kcal/mol. It can be seen from the figure that the active ingredient and the target protein can form a stable binding conformation, which verifies the accuracy of network pharmacology screening.



3096 7120　　6xvk 7120　　3096 2651　　2bdj 2651



2bdj 7120 2bdj 0422 2bdj 8206 6xvk 2651

Molecular docking diagram

## 4 DISCUSSION

4.1 Ancient records of the pathogenesis of otic neuralgia: wind, fire (heat), and stasis,wind evil is one of the causative factors and predisposing factors of otic neuralgia. The wind is active, the upper disturbance clears the orifice, "Su Wen" says: "Wind is the first of all diseases, and it can be transformed into other diseases", Wind is Yang evil, its nature is Qingyang, easy to attack Yang position, so high on the top, only the wind can be reached. Fire inflammation, clear orifice loss of nourishing, fire (heat) for Yang evil, its nature of inflammation, easy to attack Yang position, consume qi injury Yin, clear orifice loss of nourishing, earache burst. "Su Wen" says: "All the backlash belongs to fire." The functional activities of the organs and tissues of the five viscera and the whole body all depend on the nourishing of blood to play their normal functions, Wind and heat evil poison external invasion, strong pathogenic force, rapid transmission, more acute disease, evil coagulation of Qi and blood, burnt burning body fluid, glue not, lingering difficult to heal, blocking the ear meridians, blood stasis block, channel qi is not pronounced, vein obstruction and loss of nourishing, stagnation leading to pain [2] .Therefore, it adopts the method of evacuating wind evil, clearing heat and detoxifying, and also activating blood and removing stasis.

In the "Ren Zhai Zhizhi Fang Treatise Volume 19 Attached to Head Wind", other head symptoms other than headache are classified as head wind disease, which says: "Head wind is a disease, and it is not necessary to have evidence of migraine, but from the neck up, between the ears, eyes, mouth, nose and eyebrows, or there is a body that is not as good as mine, it is all gradual." [3]. Therefore, otic neuralgia belongs to the category of "Head wind disease". The cause of head wind is mostly caused by external wind evil, followed by blood stasis, phlegm turbidity, and heat evil. The viscera mostly invades the liver, followed by the spleen and kidneys [4].

4.2 Modern research shows that,nerve pain is accompanied by the release of related inflammatory factors,which can lead to nerve damage and trigger abnormal communication of multiple signaling pathways, resulting in increased ectopia, abnormal pain, and pain hyperesthesia [5].Different types of neuropathic pain differ in etiology and clinical manifestations, but one of the common mechanisms is the release of immune mediators to induce action potentials and activate nociceptive neurons;the second is peripheral sensitization, which affects the intracellular signal transduction pathway, resulting in a decrease in activation threshold and an increase in membrane excitability;the last is central sensitization involving isosynaptic and heterosynaptic promotion in the dorsal horn of the spinal cord, excitatory amino acids, ion channel dynamics and property changes [6].

4.3 Efficacy of the meridians and zang-fu organs belonging to the drug

In the formula, Rehmannia enters the blood, which has the function of nourishing blood and invigorating blood, and nourishing blood can extinguish the wind. As the old saying goes: Cure the blood before curing the wind, and then the wind will destroy itself after the blood flow is smooth. Vinegar Rhizoma Corydalis is known as the first important medicine for qi and blood activation, which has the effect of activating blood and qi, and can be used for qi stagnation in blood and blood stagnation in qi, Modern pharmacological

research has shown that this drug contains the components of tetrahydropalmatine and corydaline, which has anticonvulsant,sedative, and analgesic uses,among which L-tetrahydropalmatine achieves a strong analgesic effect by blocking D2 receptors above the spinal cord [7].The combination of Vinegar Rhizoma Corydalis fumaricus with Angelica dahurica , which has anti-inflammatory and analgesic effects, produced synergic analgesic effect, and the fraction of L-tetrahydropalmatine was increased, which enhanced the curative effect [8]. Modern studies of wild chrysanthemum and fried vitex fructus have shown that they have antibacterial,anti-inflammatory,and analgesic effects[9][10].Salvia miltiorrhizae and its tanshinone constituents and other active ingredients regulate pain-related factors, receptors, and signaling pathways in peripheral neurons and spinal cord [11]. Honeysuckle and forsythia are heat-clearing and detoxifying drugs,which have a strong anti-inflammatory effect [12] and can have a protective effect on nerves through many aspects [13] [14]; Honeysuckle can promote phagocytosis of leukocytes and inflammatory cells, and has immunomodulatory activity [12]; Extracts of Forsythia, baicalin, the main active ingredient in Scutellaria baicalensis, both have anti-inflammatory and analgesic effects on the nerves [15] [16]. The active ingredient of fried burdock has an analgesic effect, the addition of Tuckahoe and Fried atractylodes in the recipe can protect the spleen and stomach while taking medicine. The Folium isatidis are compatible with the Isatis root to clear the heat poison of qi and camp. Chinese violet is used for redness, swelling, heat and pain, dandelion heat and detoxification, modern research has both have anti-inflammatory effects, Dandelion can also improve the body's immunity [17].

4.4 Combined with the core targets of drug diseases, GO enrichment and important pathway analysis, and molecular docking results, STAT3 is composed of 750 amino acids, which has signal transduction effect and can regulate a variety of inflammatory signaling pathways[18];The activation of ERK1 and ERK2 cascades is also closely related to it[19]. Akt plays an important role in promoting cell development, maintaining cell function, and protecting cells. The expression of Akt (protein kinase B) fluctuates significantly in the nervous system when cells are stressed; Akt significantly promotes neuronal and vascular survival during apoptotic injury; Activation, phosphorylation and activity of Akt depend on the PI3-K signaling pathway. Various stimuli can activate the PI3K-Akt signaling pathway to enhance neuronal survival [20]. This pathway is an important mechanism controlling signal transduction, differentiation and axon growth [21]; Akt1 is the most expressed subtype in damaged cells [22]. CASP3 is closely related to the non-inflammatory form of programmed cell death, and one of the more important aspects of its role is to cause neurodevelopmental defects and participate in chronic neurodegenerative processes [23]。EGFR mediates or promotes the initiation and maintenance of neuropathic pain in a variety of ways, and it also mediates hyperalgesia in the PI3K-Akt signaling pathway [24]. IL1B is essential for establishing chronic inflammation, leading to neuronal dysfunction and neurodegeneration, as well as inducing an innate immune response (a rapid and coordinated cellular defense response designed to eliminate the threat posed by sterile and infectious damage) [25]; MMP9 is associated with the release of mature forms of IL1B [26].MMP9 is key to controlling synaptic plasticity and is elevated in neuropathic pain (spontaneous and provoked)[27] and is involved in the release or activation of many different bioactive molecules responsible for cell migration, differentiation, and survival,as well as immune responses, angiogenesis, or tumor microenvironment formation [26][27]. BCL2 is a mediator of apoptosis, as well as autophagy and programmed necrosis [28]. MAPK3 regulates the MAPK cascade, ERK1 and ERK2 cascades, and affects the secretion of pro-inflammatory cytokines [19]. Programmed cell death pathways (apoptosis, autophagy, and pyroptosis) during metabolic disorders affect the integrity of neuronal cells, MTOR is closely related to the above pathways, and its activation can limit apoptotic cell death in the nervous system, in which this

activation is necessary in nervous system function, and MTOR signaling dysfunction may lead to cognitive impairment and synaptic dysfunction [29]. RAS signaling within increased neurons often has neuroprotective effects, and its downstream ERK1 and ERK2 cascades affect the development of the nervous system in a variety of ways [30]. A large number of data suggest that Rap1 signaling and Ca2+ signaling are signaling pathways that are important cellular functions for synaptic plasticity and neuronal survival, and they can affect the activation of their respective pathways and control a variety of signaling [31]. The increase of TLR4 level and its pathway in nerve injury and neuroinflammation can further induce the expression of pro-inflammatory cytokines [32]; Pathophysiological changes at the peripheral, spinal, and supraspinal levels may transform acute pain states into chronic pain states if repetitive nociceptive stimuli persist, and there is clinical evidence that TLR4 plays a key role in the induction, transformation, and maintenance of chronic pain states [33]. Activation of PARP1 in relatively mild forms of oxidative stress is a reparative process that protects neurons from death [34].

## 5 CONCLUSION

dispelling wind and clearing heat, detoxifying prescription has a significant effect in the treatment of otic neuralgia, and it is not easy to recur after stopping the drug.

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**Corresponding Author:**

He Jian

The Third Affiliated Hospital of Naval Medical University, Shanghai 200000, China

E-mail：lahm00yyc9@163.com