ejpmr, 2023,10(6), 157-164

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON PATHOGENESIS OF DIABETES LEADS TO IMPAIREMENT OF AUDITORY PROCESSING AND SIGNIFICANCE OF PHYTOMEDICINES

Diksha* and Ramandeep Kaur

CT College of Pharmacy, Shahpur, Jalandhar, India, Pincode-144020.

***Corresponding Author: Diksha**

CT College of Pharmacy, Shahpur, Jalandhar, India, Pincode-144020.

Article Received on 08/04/2023 **Article Revised on 28/04/2023** **Article Accepted on 18/05/2023**

ABSTRACT

Diabetes is a group of metabolic diseases in which elevated levels of glucose in the blood are recorded. This elevation can occur due to insufficient insulin production by pancreatic cells or due to resistance to insulin produced by the pancreas. Patients with diabetes mellitus frequently have symptoms like tinnitus, hearing loss, and dizziness. Sensorineural hearing loss is usual. Although hearing loss has been linked to both type 1 and type 2 diabetes, a direct causal relationship has proven challenging to establish. Hearing loss is twice as common in people with diabetes than it is in people without the disease, and it is 30% more common in people with prediabetes. Angiopathy and neuropathy caused by diabetes mellitus have been considered important factors for the vestibular-cochlear disorders found in these patients. In this report, we will discuss hearing loss due to diabetes and herbal treatment for this hearing loss.

KEYWORDS: Diabetes mellitus, Angiopathy, Retinopathy, Neuropathy, Hearing loss.

INTRODUCTION

Diabetes is a chronic metabolic disease characterized by elevated levels of blood glucose or blood sugar for a prolonged period. It occurs when the pancreas is unable to produce a sufficient amount of insulin or due to the resistance to insulin produced or both.[1] Insulin is a hormone that is released by islet cells of the pancreas, which regulates the amount of glucose or sugar in the blood by moving it into the cells, where it can be used by the body for energy production.[2] Diabetes is classified as, type 1 diabetes, type 2 diabetes, and gestational diabetes.[3] Type 1 diabetes is also known as insulin-dependent diabetes. In this condition, the pancreas makes little or no insulin. Only 5% of diabetes patients have type 1 diabetes. It typically appears in adolescence that's why it is also known as juvenile diabetes. [4] Type 2 diabetes is also known as insulin-independent diabetes. Insulin resistance is developed in the body (that means the body doesn't respond to the insulin produced properly). It is the most common type of diabetes. About 95% of diabetes patients have type 2 diabetes.[5] Gestational diabetes is a type of diabetes that occurs only in pregnant women. It can cause health problems in both mother and baby. Those who develop gestational diabetes are at greater risk of developing type 2 diabetes later in life.[6] Excessive thirst and urination, Fatigue, weight loss, blurred vision, foot pain and numbness, persistent hunger, etc. are the common signs and symptoms in diabetic patients.[7],[8] pathophysiology of diabetes includes various environmental as well as genetic factors. Which ultimately leads to hyperglycemic conditions in the body.

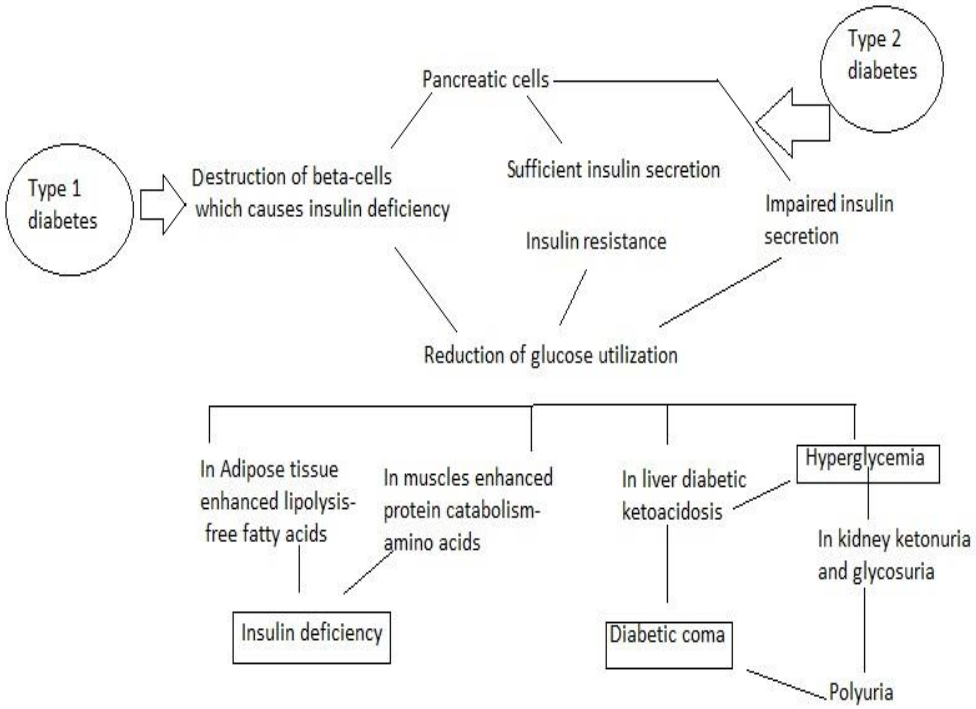


Figure 1: Pathogenesis of Diabetes and Role of insulin.

Treatment of diabetes includes controlling blood sugar through diet, the patient should avoid sugar intake, oral medications are also available such as metformin, and insulin injection and regular screening should be done to avoid complications.[9]

Hearing is the ability to sense the sounds and vibrations around us. It helps in listening to music and communicating with people.[10] An organ involved in hearing is the ear. The ear is the sensory organ that helps in hearing and maintains equilibrium. It detects the vibrations and noise from the surroundings and sends signals to the brain from where the prediction of the sound is done.[11] It is mainly divided into 3 parts, the outer ear, middle ear, and inner ear. The outer ear consists of the pinna or auricle which is the outside part of the ear, the auditory canal which connects the outer ear and middle ear, ear drum. The middle ear consists of ossicles (malleus, incus, stapes) that transmit the sound waves to the inner ear, the Eustachian tube which links the middle ear with the nose. It helps to equalize the pressure which is required for proper sound wave transfer. The Inner ear consists of the cochlea which contains nerves for hearing, the vestibule, and semicircular canals which contain receptors for equilibrium.[12] The physiology of hearing involves the striking of the eardrum by the sound waves or vibrations traveling through the auditory canal from surroundings. Then these vibrations passed through ossicles where they get amplified and then sent to the inner ear. Then these vibrations are converted to electrical impulses. These impulses are sent to the brain by the auditory nerves. Where these impulses are translated by the brain as sound.[13]

In this review article, hearing loss due to diabetes is discussed. Diabetes can lead to nerve as well as small blood vessel damage due to elevated levels of glucose in the blood. In case of a low level of blood sugar, the nerve signal traveling from the inner ear to the brain is altered which ultimately leads to hearing loss. Hearing loss is more in diabetic patients than in normal people of the same age group. Diabetic patients have a 30% higher risk of hearing loss.[14]

Diabetes

Diabetes is a major health problem arising worldwide affecting more than 400 million people.[15] Diabetes is an endocrine disorder that occurs due to less or ineffective insulin production by the islet cells of the pancreas which ultimately results in an elevated level of glucose in the blood.[16] Classification of diabetes was first given by WHO in the year 1980, which was later modified in the year 1985 as insulin-dependent diabetes [IDD] and non-insulin-dependent diabetes [NIDD].[17],[18] According to the new system of classification diabetes is of four types; type 1 diabetes, type 2 diabetes, and gestational diabetes, other specific types (monogenic type).[19] This classification is described as Type 1 diabetes or IDD: in this type of diabetes beta cells of the pancreas get destroyed due to which less amount or no insulin is produced. It is an autoimmune disease. Due to a deficiency of insulin hyperglycemic conditions developed in the body.[20] Type 2 diabetes or NIDD: in this type of diabetes body develops insulin resistance due

to which the body doesn't respond to the insulin produced by beta cells which ultimately results in hyperglycemic conditions in the body. In this condition, about 6-20 times a rise in blood glucose level can occur over the normal range.[21] Gestational diabetes: when hyperglycemic conditions developed during the pregnancy only without any previous history, known as gestational diabetes. Patients with gestational diabetes are at higher risk of developing type 2 diabetes in the future. After the delivery of the baby, gestational diabetes usually goes away.[22] Other specific types of monogenic diabetes: mutation in chromosome 12 in a hepatic transcription factor, known as hepatocyte nuclear factor-1a (HNF-1a), or genetic defects of beta cells are the most common forms of monogenic diabetes. The person identified with these genetic abnormalities is unable to convert proinsulin to insulin. Such traits get inherited in an autosomal dominant pattern. [23] Signs and symptoms of diabetes include excessive thirst and hunger, polyuria, weight loss, fatigue, and frequent urination. The presence of glucan use in more than its normal range in the blood is a major sign of diabetes.[24] Pathophysiology of diabetes includes mainly 2 conditions. First is the destruction of islet cells in the pancreas which results in less production of insulin and the second is the development of insulin resistance in the body which results in hyperglycemic conditions in the body. The flow chart given below explains the pathogenesis of diabetes:[25]

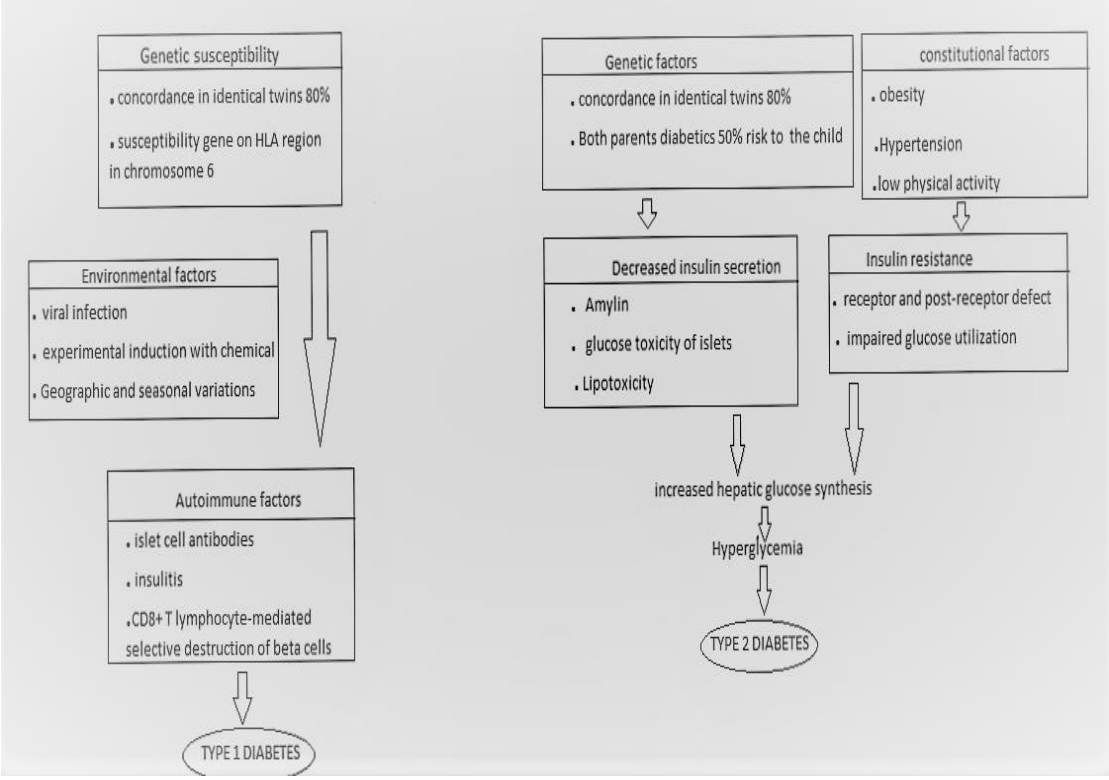
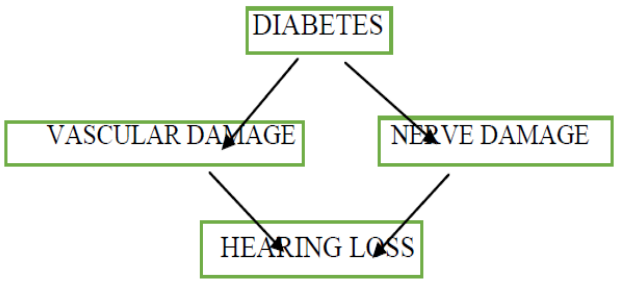


Figure 2: Factors involved in hyper-glycaemia.

Since diabetes cannot be cured but is only managed, preventing chronic complications is the major goal of treating diabetic people.[26] Diabetes is linked to numerous serious and even fatal comorbid conditions, including cardiovascular disease, kidney disease, blindness, neuropathies, and infectious complications.[27] Different complications associated with diabetes are macrovascular complications and microvascular complications. Macrovascular complications include coronary artery diseases, peripheral arterial diseases, and stroke. Microvascular complications include diabetic nephropathy, diabetic neuropathy, and retinopathy.[28]

In diabetes mellitus, neuropathy and angiopathy are frequent complications. Directly, through lowering flow in vascular routes, or even yet, due to subsequent degeneration of the 8th cranial nerve 5, angiopathy can also affect the cochlea by impairing supply by reducing transport across enlarged capillary walls.[29] In this review, hearing loss due to diabetes is mainly discussed. There are conflicting views on the pathological problems that diabetes mellitus causes in the auditory system. Since Jordao first reported it in 1857, Nageris et al. state that the link between hearing loss and diabetes mellitus has been controversial.[30] Diabetic people might experience many different types of hearing loss. One of them, a bilateral sensorineural loss that is progressive and gradual, affects high frequencies and the elderly in particular. Presbyacusis-like symptoms would occur, but more serious losses are expected as we age.[31],[32] Authors have documented hearing loss at low and medium frequencies as well as the potential for early sensorineural loss.[33],[34] Diabetes was mentioned as a potential cause of unilateral abrupt loss in certain

research, while other writers did not discover the same link.[35], [36] Type 1 and type 2 diabetes are both associated with hearing impairments, and a meta-analysis of cohorts of individuals with both types of diabetes found that the type of diabetes had no bearing on the link between diabetes and hearing impairment.[37], [38] However, none of the several studies linking hearing loss to diabetes were able to prove a causal relationship.[39] The risk factors for hearing loss are often different from those for diabetes. However, there are several risk factors that both of them share: Any insulin system dysfunction might lead to issues throughout the body. The sensory receptors and supporting cells of the cochlea, stria vascularis, and spiral ligament contain insulin receptors, glucose transporters, and insulin signaling components, which suggests that hearing and balance are susceptible to problems with glucose use. Diabetes continues to be a known risk factor for hearing loss despite the variety of diseases and onset periods associated with improper glucose processing.[40],[41],[42] Pathophysiology of hearing loss due to diabetes involves vascular damage and nerve damage.



According to Ganança, many types of hearing loss and vestibular abnormalities might result from the metabolic changes that occur in diabetes mellitus, such as hyperglycemia, hyperinsulinemia, and hypoglycemia.[43] Glucose metabolism has a great influence on the physiology of the inner ear and this stands out for its intense metabolic activity[44] According to various writers, the involvement of the blood arteries supplying the inner ear and alterations in the vascular striae in people with diabetes mellitus are clear indicators that the condition may result in hearing loss.[45] An auditory function is primarily governed by vascular and nervous tissues, and any illness that can harm these tissues' cells can harm different hearing organs. In reality, if the blood supply to the cochlea and/or nerve centers in the auditory route, including the brain, is impacted, the link between hearing and diabetes seems plausible. Both hypoglycemia and hyperglycemia can affect the cochlea's proper operation, leading to metabolic deafness since floating blood glucose are necessary for the chemical makeup of endolymph.[46],[47] Since the inner ear doesn't store energy, even little glycemic changes can affect how it functions, leading to changes. A potassium displacement from the endolymph to the perilymph and a sodium displacement in the opposite direction are brought on by metabolic changes in the inner ear. Vertigo, tinnitus, hearing loss, and fullness in the ears would all be brought on by this mechanism. Due to these inner ear vascular anomalies, it is also seen that there are fewer hair cells and less oxygen in them.[48],[49] it is thought that in addition to the peripheral nerves' sensitivity, metabolic variables, vascular problems, and other mechanisms could influence the inner ear and/or the eighth nerve and result in impaired hearing.[50] Endothelial proliferation, glycoprotein buildup in the intima, and thickening of the basal membrane of capillaries and tiny blood arteries are the hallmarks of diabetic angiopathy. A constricted vasculature or even subsequent degeneration of the eighth cranial nerve can cause angiopathy. Directly, angiopathy can affect the blood supply to the cochlea by limiting transit via thicker capillary walls.[51] It has been proposed by several authors that microangiopathy may be the cause of the functional alterations in the inner ear linked to diabetes mellitus.[52] The severity of hearing loss appears to be correlated with the advancement of the disease, which may be brought on by microangiopathic disease of the inner ear. [53] One of the most common side effects of diabetes mellitus chronic evolution is diabetic neuropathy, which is defined by the progressive degradation of nerve fiber axons.[54] The predominant electrophysiological alteration in peripheral nerves associated with diabetic neuropathy appears to be a reduction in the amplitude of sensory and motor responses. However, hyperglycemia also appears to have a demyelinating effect that slows nerve conduction velocity.[55] Herbal treatment with significant benefits for hearing loss due to diabetes.

Alpinia officinarum hance

Lesser galangal, or A. officinarum (Zingiberaceae), is said to be beneficial for treating inflammatory and cardiovascular conditions, as well as kidney dysfunction. It also has anticoagulant and anti-diabetic properties.[56] By reducing aminoglycoside-induced oxidative stress in outer and inner hair cells in vitro, galangin, the most prevalent flavonoid discovered in the rhizomes of A. officinarum, has demonstrated potential in the treatment of hearing loss.[57]

Astragalus propinquus schischkin

Deafness has been traditionally treated with A. propinquus (also known as A. membranaceous, Fabaceae) roots for hundreds of years.[58] Astragalosides are this plant's active ingredient. It has been demonstrated that pretreatment with Astragalus propinquus root extract can prevent acoustic damage.[59] By altering the expression of connexin 26 and a voltage-gated potassium channel in the stria vascularis, these changes may be connected to the control of ion transport in the inner ear. As evidenced by the reduction of oxidative stress and the expression of Cas-3 in the outer hair cells, stria vascularis, spiral ligament, and SGNs, these protective effects in the cochlea may be mediated by antioxidant and anti-apoptotic activities in numerous auditory structures.[60]

Camellia sinensis (L.) Kuntze

Because it is the most popular drink in the world, C. Sinensis (Theaceae) is widely grown all over the world. For thousands of years, green tea has been used in traditional oriental medicine to treat a variety of inflammatory diseases.[61] Epicatechin and epigallocatechin-3-gallate (EGCG) are the two main active components responsible for the protective and regenerative benefits of green tea shown against various unpleasant aural stimuli. While they both exhibit antioxidant and anti-apoptotic properties, their protective potentials and processes differ. The antioxidant EGCG has demonstrated a protective impact by inhibiting inflammatory and apoptotic pathways. It has also demonstrated a regenerative effect on hair cells by inhibiting Notch signaling, which is accomplished by inactivating γ-secretase.[62] On the other hand, epicatechin has shown that it can protect against radiation and cisplatin-induced cell death in auditory cells via inhibiting ERK.[63] The antioxidant characteristics produced in the hair cells, stria vascularis, and spiral ligament, which are mediated by a decrease in NOX3 expression, may be the source of these effects.[64]

Cornus officinalis Siebold & Zucc

Oriental medicine has long utilized the fruits of Cornaceae species C. Officinalis to cure hearing problems like tinnitus and hearing loss.[65] Organic acids and iridoids make up the majority of C. Officinalis' active ingredients. Through the stimulation of the antioxidant enzymes CAT and GPX, ursolic acid, which was extracted from the fruits of C. officinalis, has shown a protective in vitro action against hydrogen peroxide-induced damage in auditory cells.[66]

Curcuma longa L.

In Chinese and Ayurvedic Indian medicine, C. longa (Zingiberaceae) is a popular natural remedy mentioned for preventing aging and inflammatory disorders.[67] These effects have been connected to anti-apoptotic activities in hair cells, supporting tissues, and the lateral wall, as well as specific antioxidant activities mediated by increased nuclear translocation of Nrf2 and overexpression of HO-1 in SGNs. By lowering calcineurin expression, curcumin has also been demonstrated to lessen damage to fibroblasts found in the lateral wall and cochlear supporting tissues.[68]

Dioscorea japonica Thunb and Dioscorea nipponica Makino

Chinese remedies for hearing loss and tinnitus contain species of Dioscorea. Traditional uses for the yam varieties D. japonica and D. nipponica (Dioscoreaceae) include the treatment of inflammatory ailments, metabolic issues, and neurological illnesses.[69] Evidence from in vivo experiments demonstrates that the combination of both species lessens the decline in DM-induced ABR thresholds in response to clicks through promoting NGF expression.[70]

Lycium barbarum L.

L. barbarum (Solanaceae) is an herb that has been used for centuries in Chinese and Korean medicine as an immunostimulant, anti-aging agent, and to nourish the eyes, ears, liver, and kidneys.[71] When cisplatin caused cell death in HEI-OC1 cells, a pure fruit extract with a high amount of polysaccharides decreased ROS generation and preserved the mitochondrial membrane potential.[72]

Pueraria Montana var. lobata (Wild.)

Deafness and cardiovascular conditions are historically treated with P. Montana (Fabaceae) in Chinese medicine.[73] Puerarin, a significant isoflavonoid isolated from P. Montana, was shown to improve the impaired auditory function in an in vivo investigation by altering the expression of protein kinase C and the GABA receptor in the cochlear nuclear complex of the auditory central system.[74]

Reynoutria multiflora (Thunb.) Moldenke

In Korean and Chinese Traditional Medicine, R. multiflora (also known as Polygonum multiflorum Thunb; Polygonaceae) has been recommended for usage as an anti-aging agent, for treating tinnitus and hearing loss, and to nourish the liver and kidney.[75] One of the key active ingredients, resveratrol, has proven positive effects on hearing function.[76]

Salvia miltiorrhiza Bunge

In traditional Chinese and Korean medicine, S. miltiorrhiza (Lamiaceae) rhizome is a natural remedy for tinnitus and hearing loss.[77] Two distinct active compounds with potential effects on sensorineural hearing loss have been suggested by in vitro studies: one polyphenol (rosmarinic acid) and one diterpene quinone (tanshinone IIA). By decreasing the production of ROS and lipid peroxidation, up-regulating SODs, boosting the expression of Nrf2/HO-1, and inhibiting the caspase-1 downstream signaling cascade, rosmarinic acid has been shown to protect auditory cells against oxidative damage.[78] Tanshinone IIA, on the other hand, has been shown to protect cochlear cells from radiation-induced

damage through the regulation of NF-κβ translocation and p53 signaling.[79] Through the modulation of cochlear blood flow, animal studies have shown that S. miltiorrhiza extract can preserve auditory structures by lessening the ototoxic damage caused by gentamicin and cisplatin.[80]

CONCLUSION

For neuropathy, retinopathy, and nephropathy, diabetes is a significant risk factor. Diabetes is brought on by a disease involving glucose and insulin, which can directly affect the cochlea's sensory and support cells. The main ear consequences of hypertension and diabetes are macro and micro-vascular insults that result in decreased blood flow, oxygen exchange, and ion transport. It has been proposed that adopting a healthy lifestyle and eating well can stop the advancement of diabetes and hearing loss. Herbal treatment for hearing loss is discussed in this report.

REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes care, 1998; 21(9): 1414–1431.
2. Sicree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance, Diabetes Atlas International Diabetes Federation, 2006; 15-103.
3. Rawshani A, Franzén S, Eliasson B, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med, 2017; 376: 1407-18.
4. American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes. Diabetes Care, 2018; 41: S13-27.
5. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol, 2007; 27(02): 195–207.
6. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. Diabetes Care, 2003; 26(3): 917–932.
7. Hodgson MJ, Talbott E, Helmkamp JC. Diabetes, noise exposure, and hearing loss. J Occup Med, 1987; 29(7): 576–579.
8. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. Nature, 2001; 414: 799–806.
9. Bjornholm M, et al. Absence of functional insulin receptor substrate-3 (IRS-3) gene in humans. Diabetologia, 2002; 45: 1697–1702.
10. Saladin, K.S. Anatomy and Physiology: The Unity and Form of Function, Mc Graw-Hill: New York, NY, USA, 2021; 9: 578–590.
11. Unal, G.; Nain, D.; Fang, T. Generating shapes by analogies: An application to hearing aid design. Comput. Des. 2011; 43: 47–56.
12. Sachse M, Hortschitz W, Steiner H, Keplinger F. A Middle Ear Microphone Design Based on the Physiology of the Human Ear. Procedia Eng, 2011; 25: 595–598.
13. Sachse M, Hortschitz W, Steiner H. A Middle Ear Microphone Design Based on the Physiology of the Human Ear. Procedia Eng, 2011; 25: 595–598.
14. Presutti L, Anschuetz L, Rubini A, et al. The impact of the transcanal endoscopic approach and mastoid preservation on recurrence of primary acquired attic cholesteatoma. Otol Neurotol, 2018; 39(4): 445-450.
15. Milne JC, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature, 2007; 450: 712–716.
16. Storozhevykh TP, et al. Mitochondrial respiratory chain is involved in insulin-stimulated hydrogen peroxide production and plays an integral role in insulin receptor autophosphorylation in neurons. BMC Neurosci, 2007; 8: 84.
17. Verge CF, Gianani R, Kawasaki E, et al., Predicting type I diabetes in first–degree relatives using a combination of insulin, GAD, andICA512bdc/IA-2autoantibodiesDiabetes, 1996; 45: 926-33.
18. American Diabetes Association, Diagnosis, and classification of diabetes mellitus, Diabetes Care, 2014; 1.
19. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM, International Textbook of Diabetes Mellitus. 1997; 635-712.
20. Curtis, L.T, Charles A.R, 2ND, William, pharmacotherapy: A pathophysiology, Approach 7th edition, Mc Graw Hill, 2009.
21. Bertram C. KATZUNG "Basic and clinical pharmacology", 10.
22. Ueki K, et al. Positive and negative roles of p85 alpha and p85 beta regulatory subunits of phosphoinositide 3-kinase in insulin signaling. J Biol Chem, 2003; 278: 48453–48466.
23. Cho H, et al. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta) Science, 2001; 292: 1728–1731.
24. Sntoskar RS, Bhandarkar SD, Rege N Nirmala. Pharmacology and pharmacotherapeutics, 2007.
25. Goodpaster BH, et al. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab, 2001; 86:5755–5761.
26. Cheng Z, White MF. Targeting FOXO1 from the concept to metabolic diseases–lessons from mouse models. Antioxid Redox Signal, 2010 doi: 10.1089/ars.2010.3370.
27. van der Horst A, Burgering BM. Stressing the role of FoxO proteins in lifespan and disease. Nat Rev Mol Cell Biol, 2007; 8: 440–450.
28. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev Suppl, 2013; 93: 137-88.
29. Matough FA, Alwahaibi N, Mohamed J. The Role of Oxidative Stress and Antioxidants in Diabetic Complications. Sultan Qaboos Univ Med J, 2012; 12: 5-18.
30. Duby JJ, Campbell RK, Rasmussen KA. Diabetic neuropathy: an intensive review. Am J Health Syst Pharm, 2004; 61: 160-73.

31. Singh VP, Bali A, Singh N. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol, 2014: 18: 1-14.
32. Geraldes P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. Circ Res, 2010; 106: 1319-31.
33. Tay HL, Ray N, Fronntko NJ. Diabetes mellitus and hearing loss. Clin Otolaryngol, 1995; 20: 130-4.
34. Horikawa C, Kodama S, Tanaka S. Diabetes and risk of hearing impairment in adults: a meta-analysis. J. Clin. Endocrinol. Metab, 2013; 98: 51–58.
35. Agrawal Y, Carey JP, Minor LB. Diabetes, vestibular dysfunction, and falls: analyses from the National Health and Nutrition Examination Survey. Otol. Neurotol, 2010; 31: 1445–1450.
36. Degerman, E., Rauch, U., Lindberg, S. Expression of insulin signaling components in the sensory epithelium of the human saccule. Cell Tissue Res, 2013; 52: 469–478.
37. Huerzeler N, Petkovic V, Wright MB. Insulin receptor and glucose transporters in the mammalian cochlea. Audiol. Neurootol, 2019; 24: 65–76.
38. Vaughan N, McDermott D. Diabetes and hearing loss: exploring connections. Hear Health, 2003; 19(3): 37-43.
39. Vaughan N, James K, McDermott D. A 5-year prospective study of diabetes and hearing loss in a veteran population. Otol Neurotol, 2006; 27(1): 37-43.
40. Kakarlapudi V, Sawyer R, Staecker H. The effect of diabetes on sensorineural hearing loss. Otol Neurotol, 2003; 24(3): 382-6.
41. Lasisi OA, Nwaorgu OGB, Bella AF. Cochlear vestibular complications of diabetes mellitus in Ibadan, Nigeria. Int Congress Series, 2003; 12 (40): 1325-1328.
42. Zhang MH, Zhang L. A study on the diagnostic value of brain stem auditory evoked potentials in diabetic deafness. Journal of Clinical Internal Medicine, 2005; 22 (8): 563.
43. Ganança MM & Fukuda Y. Otorrinolaringologia. Rio de Janeiro: Guanabara Koogan, 1995.
44. Albernaz PLM. Doenças metabólicas da orelha interna. RBM – Otorrinolaringologia, 1995; 1: 18-22.
45. Fukushima H, Cureoglu S, Schachern PA, et al. Effects of type 2 diabetes mellitus on cochlear structure in humans. Arch Otolaryngol Head Neck Surg, 2006; 132 (9): 934-938.
46. Lin Y, Qiu JH, Qiao L, et al. Influence of ANF on cochlear microcirculation. Journal of Audiology and Speech Pathology, 2006; 5: 347-350.
47. Jiang HQ, Wang ZM, Shen YZ, et al. Culture, identification and ultrastructural observation of cochlear proliferative cells in newborn rats. Chinese Journal of Otolaryngology-Head and Neck Surgery, 2007; 6: 42- 47.
48. Sakuta H, Suzuki T, Yasuda H, Ito T. Type 2 diabetes and hearing loss in personnel of the Self-Defense Forces. Diabetes Research and Clinical Practice, 2007; 75: 229-34.
49. Pudar G, Vlaski L, Filipovic D. Correlation of hearing function findings in patients suffering from diabetes mellitus type 1 regarding age and gender. Med Pregl, 2009; 9: 395-401
50. Akinpelu OV, Mujica-Mota M, Daniel SJ. Is type 2 diabetes mellitus associated with hearing loss? A systematic review and meta-analysis. Laryngoscope, 2014; 124: 767–776.
51. Taylor IG, Irwin J. Some audiological aspects of diabetes mellitus. J Laryngol Otol, 1978; 92(2): 99-113.
52. Herrmann DN, Ferguson ML, Logigian EL. Conduction slowing in diabetic distal polyneuropathy. Muscle Nerve. 2002; 26:232-7
53. Fowler PD, Jones NS. Diabetes and hearing loss. Clinical Otorrinolaringol. & allied sciences, 1999; 24(1): 3-8.
54. Dalton DS, Klein R, Moss SE. Association of NIDDM and hearing loss; Diabetes Care, 1998; 21(9): 1540-4.
55. Nageris B, Hadar T, Feinmesser M. Cochlear histopathologic analysis in diabetic rats. The American Journal of Otology, 1998; 19: 63-5.
56. Unnisa A, Parveen TD. Anti-inflammatory and acute toxicity studies of the extracts from the rhizomes of Alpinia galanga Wild. Der Pharm Sin, 2011; 2(2): 361-7
57. Roy SK, Pahwa S, Jachak SM. Phenylpropanoids of Alpinia galanga as efflux pump inhibitors in Mycobacterium smegmatis mc2 155. Fitoterapia, 2012; 83(7): 1248-55.
58. Xiao K, Cao ST, le F J. Anemonin improves intestinal barrier restoration and influences TGF-beta1 and EGFR signaling pathways in LPS-challenged piglets. Innate Immun, 2016; 22(5): 344–52.
59. Greig CJ, Cowles RA. Muscarinic acetylcholine receptors participate in small intestinal mucosal homeostasis. J Pediatr Surg, 2017; 52(6): 1031–4.
60. Zhang K, Pugliese M, Pugliese A. Biological active ingredients of traditional Chinese herb Astragalus membranaceous on the treatment of diabetes: a systematic review. Mini Rev Med Chem, 2015; 15(4): 315–29.
61. Manir MM, Kim JK, Lee BG. Tea catechins and flavonoids from the leaves of Camellia sinensis inhibit yeast alcohol dehydrogenase. Bioorganic and Medicinal Chemistry, 2012; 20: 2376-2381.
62. Matsubara S, Shibata H, Ishikawa. Suppression of Helicobacter pylori-induced gastritis by green tea extract in Mongolian gerbils. Biochemical and Biophysical Research Communication, 2003; 310: 715-719.
63. Mondal TK, Bhattacharya A, Laxmikumaran M. Recent advances of tea (Camellia sinensis) biotechnology. Plant Cell Tissue and Organ Culture, 2004; 76: 195-254.

64. Pastore RL, Fratellone P. Potential health benefits of green tea (Camellia sinensis): a narrative review. Diet and Nutrition, 2006; 2: 531-539.
65. Song XY, Chen Q, Qi XY. Effect of Liuwei Dihuang pill on erythrocyte aldose reductase activity in early diabetic nephropathy patients. Chin J Integr Tradit West Med, 2004; 24: 1087–1090.
66. Chen H, Zhang HJ, Zhang MJ. Orthogonal test for optimization of extraction condition for volatile components of Cornus officinalis and extract analysis by GC–MS. J Third Mil Med Univ, 2007; 29: 1079–1082.
67. Chowdhury JU, Nandi NC, Bhuiyan MNI. Essential oil constituents of the rhizomes of two types of Curcuma longa of Bangladesh. Bangladesh J Sci Ind Res, 2008; 43: 259-266.
68. Saraf S, Chhabra SK, Kaur CD. Development of photochemoprotective herbs containing cosmetic formulations for improving skin properties. J Cosmet Sci, 2012; 63(2): 119-31.
69. Tao YY, Zhang B, Yu HS, et al. Production and properties of saikosaponin- glycosidase. J Dalian Inst Light Ind, 2007; 26(2): 120–123.
70. Tang YN, Yi T, Chen HM, et al. Quantitative comparison of multiple components in Dioscorea nipponica and D. panthaica by ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. Phytochem Anal, 2013; 24: 413–422.
71. Machefer G, Groussard C, Vincent S, et al. Multivitamin-mineral supplementation prevents lipid peroxidation during "The Marathon des Sables". Journal of American College of Nutrition, 2007; 26: 111−120.
72. Ni H, Qing D, Kaisa S. The study on the effect of LBP on cleaning hydroxygen free radical by EPR technique. Zhong Yao Cai (Journal of Chinese Medicinal Materials), 2004; 27(8): 599−600.
73. Tungmunnithum D, Thongboonyou A, Pholboon A. Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview. Medicines, 2018; 5: 93.
74. Wong KH, Li GQ, Li KM. Kudzu root: Traditional uses and potential medicinal benefits in diabetes and cardiovascular diseases. J. Ethnopharmacol, 2011; 134: 584–607.
75. Tu C, Niu M, Wei AW, et al. Susceptibility-Related Cytokine Panel for Prediction of Polygonum Multiflorum-Induced Hepatotoxicity in Humans. J. Inflamm. Res, 2021; 14: 645–655.
76. Xing Y, Wang L, Wang C, et al. Pharmacokinetic Studies Unveiled the Drug-Drug Interaction between Trans-2,3,5,4'-tetrahydroxystilbene-2-O-β-d-glucopyranoside and Emodin that May Contribute to the Idiosyncratic Hepatotoxicity of Polygoni Multiflori Radix. J. Pharm. Biomed. Anal, 2019; 164: 672–680.
77. Cui Q., Yang D.-H., Chen Z.-S. Special issue: natural products: anticancer and beyond. Molecules, 2018; 23(6):1246–1249.
78. Pashirzad M, Johnston TP, Sahebkar A. Therapeutic effects of polyphenols on the treatment of colorectal cancer by regulating Wnt beta-catenin signaling pathway. Journal of Oncology, 2021; 2021: 12.
79. Morrison KC, Hergenrother PJ. Natural products as starting points for the synthesis of complex and diverse compounds. Natural Product Reports, 2014; 31(1): 6–14.
80. Chen W, Chen G. Danshen (Salvia miltiorrhiza Bunge): a prospective healing sage for cardiovascular diseases. Current Pharmaceutical Design, 2017; 23(34): 5125–5135.