CLINICAL VIGNETTE

Integrative East-West Approach to the Treatment of Primary Subjective Tinnitus

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Introduction

Tinnitus refers to the perception of sound without the presence of an acoustic stimulus. Rather than a disease process, tinnitus is a symptom that can be associated with many causes with aggravating cofactors.[1] According to the American Tinnitus Association, an estimated 50 million people in the U.S. have chronic tinnitus (> 6 months), with a prevalence of 10-15% in adults.[2,3] Approximately 20% of adults who experience tinnitus will require clinical intervention given the interference with the quality of life (QOL).[4] There is currently no definitive treatment for primary subjective tinnitus with most interventions targeting symptom reduction.[3] We describe a patient with chronic primary subjective tinnitus successfully treated with an integrative East-West medical approach.

Case Presentation

A 47-year-old man with eczema, chronic neck tension, and primary insomnia presented with a two-year history of bilateral tinnitus, worse in the left ear.

Initially, the tinnitus was intermittent with short-lived episodes lasting hours. He noticed the bilateral tinnitus became more constant two years ago with left ear ringing greater than the right. Symptoms were worse watching loud movies and associated with brief otalgia. He denied upper respiratory illness, auricular pain, neurological symptoms, disequilibrium, ototoxic medications, trauma/injury or any other identifiable causes for his tinnitus. He saw ENT and extensive testing was negative for sensorineural hearing loss, eustachian tube dysfunction, or spasm of the inner ear musculature. MRI of the head and auditory canal showed no acute findings. Cervical X-rays showed a mild reversal of cervical lordosis and mild cervical degenerative disc disease without evidence of stenosis. He reported occasional nighttime bruxism with masseter discomfort; however, imaging found no evidence of TMJ related OA or disc displacement. Given the negative evaluation for direct etiologies he was given a diagnosis of primary idiopathic tinnitus.

He tried over the counter vitamin supplementations such as lipoflavinoids, and high dose gingko balboa without improvement. Use of white noise machine at night provided only mild relief. He was offered an off-label trial of a tricyclic antidepressant for the tinnitus but declined prescription medication therapy.

The patient presented to the UCLA Center for East-West Medicine clinic. At the time, he had persistent tinnitus in his left ear and intermittent tinnitus in the right ear. He was not able to identity exacerbating causes but on further review reported stress intensified the tinnitus. He described the tinnitus as constant, high frequency, non-pulsatile, and worse at night with sleep. His history of insomnia preceded his tinnitus, but the tinnitus exacerbated his insomnia. Two years prior when his tinnitus became more constant, he had just transitioned to a new job as a project manager with increased stress. Family stress also increased over the last few years. He drank about two alcoholic beverages a night for relaxation and denied use of tobacco, marijuana or recreational drugs. He reported significant daily computer use associated with chronic neck tension.

During the initial examination, he had shoulder forward posture with significant tension over the cervical/thoracic muscle groups most prominent over the trapezius and levator scapulae bilaterally. Exam also noted tight masseter muscles. He reported bruxism during times of stress but denied TMJ arthralgia.

He was seen a total of seven times within six months. A holistic treatment regimen was outlined including acupuncture/ acupressure, trigger point injection (TPI), stretching with improved ergonomics, dietary recommendations, along with an overall emphasis on stress reduction. During the first visit, procedure-based therapy was employed toward active trigger points found on the neck and shoulder regions, which were injected with 0.5mL of Lidocaine 1% (see Figure 1 for muscle groups). Acupuncture was utilized across the following points: Large Intestine 4, 11, Liver 3, Triple burner 21, 5, Small Intestine 19, Gallbladder 2, 20, 21, 43, Governing Vessel 20, and Yintang.

At the second visit, he reported minimal improvement. The Tinnitus Handicap Inventory (THI see Figure 2) was employed, with a score of 56 indicating a moderate-severe daily life impact of disability perceived by the patient. Procedure based therapy with acupuncture and TPIs were continued. Deep breathing, meditation, along with trail of magnesium supplementation and chrysanthemum tea were recommended to assist with stress and insomnia. The importance of work place ergonomics and stretching techniques were also taught to the patient, along with use of a TENS unit over specific cervical and shoulder muscle groups. Over the next several visits, he incorporated the self-care regimen, and decreased alcohol intake with improvements

in his neck/shoulder pain and sleep quality. Repeat THI showed a decrease to a score of 40 (indicating moderate severity).

At the fifth visit, in addition to acupuncture and TPIs, he was further counseled on stress management as part of the root issue contributing to increased sympathetic drive and tinnitus. He decided to enroll in family therapy to help improve family communication. During seventh visit, he noted significant improvement in the quality of his tinnitus with less impact on his daily life and improved sleep. Repeat THI was performed which indicated a score of 36 (mild disturbance on daily life). Through the course of his treatment, he continued with TPI and acupuncture, which along with the self-care regimen drastically improved his cervical neck and shoulder pain. Overall, he felt more energized, experienced improved sleep, decreased daily stress and noticed a significant decrease in the intensity of his tinnitus.

Discussion

The history to define and treat tinnitus can be dated back to ancient Egypt where the early Egyptian papyrus on medical knowledge describes tinnitus as a "bewitched ear".[5] Circa 2500 B.C. Egyptian documents depict infusion of oils into the ear with the goal of reducing the intensity of ringing.[6] Despite centuries of medical documentation and treatments, tinnitus is still commonplace in society today and its treatment remains elusive.

Tinnitus is a symptom with multiple causes and aggravating cofactors. In the simplest terms, it is important to discern between subjective and objective tinnitus. Objective tinnitus can be perceived by both the patient and examiner and is usually from a vascular source or structures near or within the ear.[7,8] Objective tinnitus is rare comprising less than 5% of tinnitus cases in the US.[8-10] The great majority of tinnitus is subjective perceived only by the patient.[1] Subjective tinnitus can be further classified as primary (also referred to as idiopathic) or secondary that correlates with a specific underlying cause.[11] Both may or may not be associated with SNHL.[1] The case presented illustrates a case of primary tinnitus not associated with SNHL with mood and cervical somatosensory components.

Primary tinnitus is challenging for both patients and treating practitioners given the lack of specified etiology and subjective nature. The Tinnitus Handicap Index (see Figure 2) is a useful tool that takes focus away from the attributes of the tinnitus such as intensity, and quantitates the degree of disability and impact on QOL.[12,13] The THI provides insight on the effects of tinnitus on mood, sleep, and stress, which are known to be co-morbid conditions in many patients. There is ample research correlating chronic stress and co-morbid mood disorders such as anxiety and depression as co-factors exacerbating tinnitus severity and increasing THI scores when poorly controlled.[14,15] Similarly, better controlled anxiety and depression are directly correlated with a decrease in tinnitus severity.[15] Emotional and physical exhaustion from stress is a strong predictor of tinnitus severity, and many patients report the incidence of the tinnitus coinciding with a stressful life event.[16] Stress management strategies when included in the care of patients with primary tinnitus have reported improved THI scores and impact on QOL.[16,17] Lastly, tinnitus creates a vicious cycle in relation to insomnia. The noise attributed with tinnitus can worsen insomnia causing further sleep deprivation and further deterioration on QOL.[10,18] Thus, focus on insomnia through lifestyle modifications, white noise machines, and sleep hygiene is imperative in the medical care of tinnitus as improved sleep is correlated with lower THI scores.[18,19]

More recently, cervical somatic tinnitus has been related to cervical and temporal mandibular joint dysfunction. The concept is that cervical/TMJ disorders can modulate brainstem structures and evoke inputs from the somatosensory and auditory system with alterations in neuronal inputs altering tinnitus.[20] While the exact pathophysiology is ill defined, somatic tinnitus is defined as tinnitus in which factors linked to forceful muscle contractions of the head and neck, increased local muscle tension, or certain movements of the head/neck can modulate the psychoacoustic attributes of the tinnitus.[21-23] Growing literature supports initial treatment of somatosensory tinnitus should relax muscle tension in the jaw and neck.[21] Relaxation of cervical-occipital and masseter muscle tension has significantly decreased the intensity of cervical somatic tinnitus.[24,25] Furthermore, the relationship between myofascial trigger points (MTP) deactivation and tinnitus relief can be traced back to the 1960s when Janet Travell demonstrated improvement in tinnitus with injection of local MTP.[26] Many small-randomized control trials have reported improvement in cervical somatosensory tinnitus with MTP therapy.[23,27-29]

A 2012 Cochrane review of acupuncture for the treatment of subjective tinnitus could not draw definitive conclusion in the support of acupuncture.[30] Some limitations cited included size of RCTs, style of acupuncture utilized, etiology of the tinnitus and variable reporting of outcomes due to the subject nature of the disease. Despite these challenges, a large number of smaller RCTs supported acupuncture as safe and effective treatment to reduce intensity and improve QOL for patient with subjective tinnitus.[12,31] Acupuncture as a traditional Chinese medicine (TCM) approach has been used to treat tinnitus for centuries using pattern diagnosis to identify and treat the underlying cause.[32] Studies report stimulation of acupuncture points release neurotransmitters such as serotonin, oxytocin, and endorphins in the CNS as well as provide improved stress regulation and localized muscle relaxation.[31,32] Directed needle selection with acupuncture in the treatment of tinnitus has been shown to increase blood flow to the auditory cortex on fMRI with possible modulation of afferent neuronal activity.[33,34] Improved management of co-morbid conditions such as anxiety, insomnia and cervical myofascial tension also results in decreased THI scores and less distress. The role of acupuncture in assisting with stress, anxiety, and cervical muscle strain is well documented and recommended by the World Health Organization (WHO).[35] Utilization of acupuncture for the treatment of co-morbid conditions in tinnitus can decrease disease burden and improve QOL.

This patient suffered from chronic subjective primary tinnitus with cervical somatic, mood, and stress components. Our approach was integrative driven treatment to reduce disease burden. Acupuncture and MTP procedure-based therapy along with stretches and ergonomic changes helped address the cervical somatic component. Magnesium assisted with insomnia, muscle cramps/tension, and anxiety as prior research document hypomagnesemia leads to increase pro-inflammatory cytokines and propensity toward oxidative stress.[36-38] Magnesium also assisted with insomnia and cervical strain, which was effective in our patient. Traditional calming teas such as chrysanthemum help mitigate the stress response. Early in vivo studies suggest chrysanthemum may alter the regulation of inflammation along with having anti-anxiolytic and anti-apoptotic effects.[39,40] Additionally, mindfulness practices impacted stress, sleep and anxiety, improved sleep hygiene and empowered him to resolve familial stressors. Prior directed treatments had failed to provide substantial relief for our patient, but through an integrative approach of addressing the tinnitus along with aggravating co-morbid conditions there was a significant improvement in his THI scores and disease burden.

Conclusion

Subjective tinnitus is difficult and challenging to treat for both patients and clinicians. Currently, there is no effective or standardized established treatment for managing primary idiopathic tinnitus. Current non-invasive conventional treatments focus primarily on masking tinnitus with other auditory inputs and the usual medications and supplements that are recommended have mixed results. Instead, focusing on a thorough history, physical exam, assessing for co-morbid conditions, along with employing tools such as the THI to delineate areas of distress caused by tinnitus can allow clinicians to better focus interventions. We proposed a more comprehensive integrative approach incorporating acupuncture, MTP injections, self-acupressure, and ergonomics, with directed lifestyle modifications on co-morbid aggravating conditions to decrease disease and improve QOL with primary subjective tinnitus.

Figures

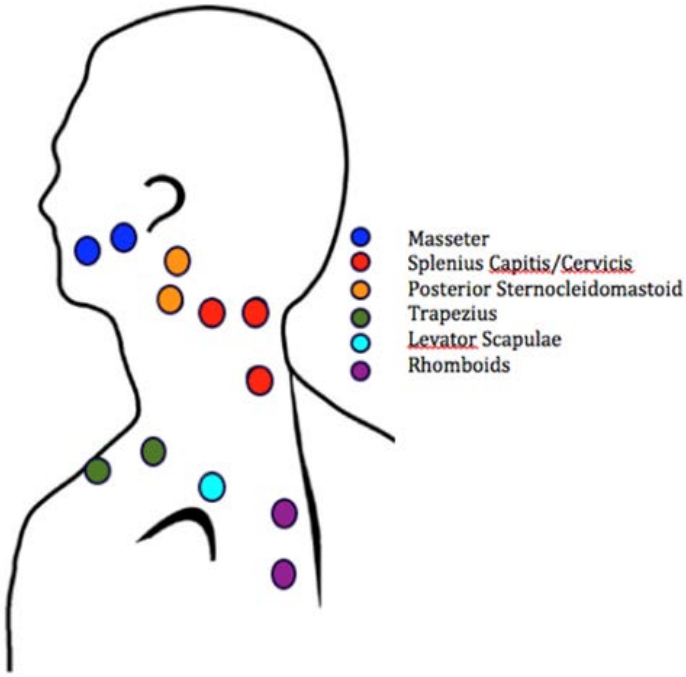
Figure 1. Tinnitus Handicap Inventory (THI). A self-administered test that allows providers to better assess the degree of distress suffered from tinnitus on daily life.

THI SCORE	DEGREE OF CONDITION
0-16	Slight or no handicap (Grade 1)
18-36	Mild Handicap (Grade 2)
38-56	Moderate Handicap (Grade 3)
58-76	Severe Handicap (Grade 4)
78-100	Catastrophic Handicap (Grade 5)

Score	4	2	0
1. Because of your tinnitus, is it difficult for you to concentrate?	YES	SOMETIMES	NO
2. Does the volume of your tinnitus make it difficult for you to hear others?	YES	SOMETIMES	NO
3. Does your tinnitus make you angry?	YES	SOMETIMES	NO
4. Does your tinnitus make you feel confused?	YES	SOMETIMES	NO
5. Because of your tinnitus, do you feel hopeless?	YES	SOMETIMES	NO
6. Do you complain a great deal about your tinnitus?	YES	SOMETIMES	NO
7. Because of your tinnitus, do you have trouble falling asleep?	YES	SOMETIMES	NO
8. Do you feel as though you cannot escape your tinnitus?	YES	SOMETIMES	NO
9. Does your tinnitus interfere with your ability to enjoy your social activities?	YES	SOMETIMES	NO
10. Because of your tinnitus, do you feel frustrated?	YES	SOMETIMES	NO
11. Because of your tinnitus, do you feel that you have significant disease	YES	SOMETIMES	NO
12. Does your tinnitus make it difficult for you to enjoy life?	YES	SOMETIMES	NO
13. Does your tinnitus interfere with your job or household activities?	YES	SOMETIMES	NO
14. Because of your tinnitus, do you find that you are often irritable?	YES	SOMETIMES	NO
15. Because of your tinnitus, is it difficult for you to read?	YES	SOMETIMES	NO
16. Does your tinnitus make you upset?	YES	SOMETIMES	NO
17. Does your tinnitus impair your relationships with family and friends?	YES	SOMETIMES	NO
18. Do you find it difficult to focus your attention away from your tinnitus?	YES	SOMETIMES	NO
19. Do you feel that you have no control over your tinnitus?	YES	SOMETIMES	NO
20. Because of your tinnitus, do you often feel tired?	YES	SOMETIMES	NO
21. Because of your tinnitus, do you feel depressed?	YES	SOMETIMES	NO
22. Does your tinnitus make you feel anxious?	YES	SOMETIMES	NO
23. Do you feel that you can no longer cope with your tinnitus?	YES	SOMETIMES	NO
24. Does your tinnitus get worse when you are stressed?	YES	SOMETIMES	NO
25. Does your tinnitus make you feel apprehensive?	YES	SOMETIMES	NO

This Tinnitus Handicap Inventory was adapted/modified from the American Tinnitus Association THI (Original Source).

Figure 2. Location of trigger point injection sites over different muscle groups. Not all muscle groups were injected in one visit. Injections sites were decided based on exam and active myofascial trigger points.



REFERENCES

1. **Tunkel DE, Bauer CA, Sun GH, Rosenfeld RM, Chandrasekhar SS, Cunningham ER Jr, Archer SM, Blakley BW, Carter JM, Granieri EC, Henry JA, Hollingsworth D, Khan FA, Mitchell S, Monfared A, Newman CW, Omole FS, Phillips CD, Robinson SK, Taw MB, Tyler RS, Waguespack R, Whamond EJ**. Clinical practice guideline: tinnitus. *Otolaryngol Head Neck Surg*. 2014 Oct;151(2 Suppl):S1-S40. doi: 10.1177/0194599814545325. PMID: 25273878.
2. **Hoffman HJ, Reed GW**. Epidemiology of tinnitus. In: Snow JB, ed. *Tinnitus: Theory and Management*. Lewiston, NY: BC Decker; 2004:16-41.
3. **Shargorodsky J, Curhan GC, Farwell WR**. Prevalence and characteristics of tinnitus among US adults. *Am J Med*. 2010 Aug;123(8):711-8. doi: 10.1016/j.amjmed.2010.02.015. PMID: 20670725.
4. **Henry JA, Zaugg TL, Myers PJ, Schechter MA**. The role of audiologic evaluation in progressive audiologic tinnitus management. *Trends Amplif*. 2008 Sep;12(3):170-87. doi: 10.1177/1084713808319941. Epub 2008 Jul 15. PMID: 18628281; PMCID: PMC4134888.
5. **Heller AJ**. Classification and epidemiology of tinnitus. *Otolaryngol Clin North Am*. 2003 Apr;36(2):239-48. doi: 10.1016/s0030-6665(02)00160-3. PMID: 12856294.
6. **Stephens SD**. The treatment of tinnitus--a historical perspective. *J Laryngol Otol*. 1984 Oct;98(10):963-72. doi: 10.1017/s0022215100147802. PMID: 6387016.
7. **Han BI, Lee HW, Kim TY, Lim JS, Shin KS**. Tinnitus: characteristics, causes, mechanisms, and treatments. *J Clin Neurol*. 2009 Mar;5(1):11-9. doi: 10.3988/jcn.2009.5.1.11. Epub 2009 Mar 31. PMID: 19513328; PMCID: PMC2686891.
8. **Baguley DM**. Mechanisms of tinnitus. *Br Med Bull*. 2002;63:195-212. doi: 10.1093/bmb/63.1.195. PMID: 12324394.
9. **Sismanis A**. Pulsatile tinnitus: contemporary assessment and management. *Curr Opin Otolaryngol Head Neck Surg*. 2011 Oct;19(5):348-57. doi: 10.1097/MOO.0b013e3283493fd8. PMID: 22552697.
10. **Folmer RL, Martin WH, Shi Y**. Tinnitus: questions to reveal the cause, answers to provide relief. *J Fam Pract*. 2004 Jul;53(7):532-40. PMID: 15251092.
11. **Yew KS**. Diagnostic approach to patients with tinnitus. *Am Fam Physician*. 2014 Jan 15;89(2):106-13. PMID: 24444578.
12. **Newman CW, Sandridge SA, Bolek L**. Development and psychometric adequacy of the screening version of the tinnitus handicap inventory. *Otol Neurotol*. 2008 Apr;29(3):276-81. doi: 10.1097/MAO.0b013e31816569c4. PMID: 18277308.
13. **Lee JH, Ra JJ, Kim YH**. Adequacy of the Simplified Version of the Tinnitus Handicap Inventory (THI-S) to Measure Tinnitus Handicap and Relevant Distress. *Korean J Audiol*. 2014 Apr;18(1):19-27. doi: 10.7874/kja.2014.18.1.19. Epub 2014 Apr 14. PMID: 24782947; PMCID: PMC4003733.
14. **Rogha M, Rezvani M, Khodami AR.** The effects of acupuncture on the inner ear originated tinnitus. *J Res Med*

Sci. 2011 Sep;16(9):1217-23. PMID: 22973392; PMCID: PMC3430048.

15. **Durai M, Searchfield G**. Anxiety and depression, personality traits relevant to tinnitus: A scoping review. *Int J Audiol*. 2016 Nov;55(11):605-15. doi: 10.1080/14992027.2016.1198966. Epub 2016 Jul 7. PMID: 27387463.
16. **Hébert S, Canlon B, Hasson D.** Emotional exhaustion as a predictor of tinnitus. *Psychother Psychosom*. 2012; 81(5):324-6. doi: 10.1159/000335043. Epub 2012 Aug 1. PMID: 22854311.
17. **Baigi A, Oden A, Almlid-Larsen V, Barrenäs ML, Holgers KM**. Tinnitus in the general population with a focus on noise and stress: a public health study. *Ear Hear*. 2011 Nov-Dec;32(6):787-9. doi: 10.1097/AUD.0b013e31822229bd. PMID: 21716113.
18. **Folmer RL, Griest SE**. Tinnitus and insomnia. *Am J Otolaryngol*. 2000 Sep-Oct;21(5):287-93. doi: 10.1053/ajot.2000.9871. PMID: 11032291.
19. **Wu V, Cooke B, Eitutis S, Simpson MTW, Beyea JA.** Approach to tinnitus management. *Can Fam Physician*. 2018 Jul;64(7):491-495. PMID: 30002023; PMCID: PMC6042678.
20. **Bousema EJ, Koops EA, van Dijk P, Dijkstra PU**. Association Between Subjective Tinnitus and Cervical Spine or Temporomandibular Disorders: A Systematic Review. *Trends Hear*. 2018 Jan-Dec;22: 2331216518800640. doi: 10.1177/2331216518800640. PMID: 30269683; PMCID: PMC6168723.
21. **Sanchez TG, Rocha CB**. Diagnosis and management of somatosensory tinnitus: review article. *Clinics (Sao Paulo)*. 2011;66(6):1089-94. doi: 10.1590/s1807-59322011000600028. PMID: 21808880; PMCID: PMC3129953.
22. **Sanchez TG, Guerra GC, Lorenzi MC, Brandão AL, Bento RF**. The influence of voluntary muscle contractions upon the onset and modulation of tinnitus. *Audiol Neurootol*. 2002 Nov-Dec;7(6):370-5. doi: 10.1159/000066155. PMID: 12401968.
23. **Sajadi S, Forogh B, ZoghAli M**. Cervical Trigger Point Acupuncture for Treatment of Somatic Tinnitus. *J Acupunct Meridian Stud*. 2019 Dec;12(6):197-200. doi: 10.1016/j.jams.2019.07.004. Epub 2019 Jul 29. PMID: 31369860.
24. **Björne A**. Assessment of temporomandibular and cervical spine disorders in tinnitus patients. *Prog Brain Res*. 2007;166:215-9. doi: 10.1016/S0079-6123(07)66019-1. PMID: 17956785.
25. **de Felício CM, Melchior Mde O, Ferreira CL, Da Silva MA.** Otologic symptoms of temporomandibular disorder and effect of orofacial myofunctional therapy. *Cranio*. 2008 Apr;26(2):118-25. doi: 10.1179/crn.2008.016. PMID: 18468271.
26. **Travell J**. Temporomandibular joint pain referred from muscle of the head and neck. *Journal Prosthetics Dentistry*. 1960;10:745–63.
27. **Rocha CB, Sanchez TG**. Efficacy of myofascial trigger point deactivation for tinnitus control. *Braz J Otorhinolaryngol*. 2012 Dec;78(6):21-6. doi: 10.5935/1808-8694.20120028. PMID: 23306563.
28. **Sanchez T**. Trigger points: occurrence in tinnitus patients and ability to modulate tinnitus. *Otolaryngology - Head and Neck Surgery*. 2003;129(2):P241.
29. **Eriksson M, Gustafsson S, et al**. Tinnitus and trigger points: a randomized cross-over study. *Proceedings of the Fifth International Tinnitus Seminar*. Portland: 1995. pp. 81–3.
30. **Kim JI, Choi JY, Lee DH, Choi TY, Lee MS, Ernst E**. Acupuncture for the treatment of tinnitus: a systematic review of randomized clinical trials. *BMC Complement Altern Med*. 2012 Jul 17;12:97. doi: 10.1186/1472-6882-12-97. PMID: 22805113; PMCID: PMC3493359.
31. **Naderinabi B, Soltanipour S, Nemati S, Saberi A, Parastesh S.** Acupuncture for chronic nonpulsatile tinnitus: A randomized clinical trial. *Caspian J Intern Med*. 2018 Winter;9(1):38-45. doi: 10.22088/cjim.9.1.38. PMID: 29387318; PMCID: PMC5771359.
32. **Xie H, Li X, Lai J, Zhou Y, Wang C, Liang J**. Effectiveness of De Qi during acupuncture for the treatment of tinnitus: study protocol for a randomized controlled trial. *Trials*. 2014 Oct 15;15:397. doi: 10.1186/1745-6215-15-397. PMID: 25319802; PMCID: PMC4209070.
33. **Xia Y, Cao X, Wu G, Cheng J**. *Acupuncture Therapy for Neurological Diseases: A Neurobiological View*; 1st ed. London: Springer; 2010. p. 86
34. **Hui KK, Liu J, Makris N, Gollub RL, Chen AJ, Moore CI, Kennedy DN, Rosen BR, Kwong KK**. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. *Hum Brain Mapp*. 2000;9(1):13-25. doi: 10.1002/(sici)1097-0193(2000)9:1<13::aid-hbm2>3.0.co;2-f. PMID: 10643726; PMCID: PMC6871878.
35. The World Health Organization recommends acupuncture for over 100 conditions. Holistic Health Oxford | Acupuncture and Chinese herbal medicine in Oxford. Published August 29, 2017. https://holistic-health.org.uk/world-health-organisation-recommends-acupuncture-100-conditions/.
36. **Rude RK, Wei L, Norton HJ, Lu SS, Dempster DW, Gruber HE**. TNFalpha receptor knockout in mice reduces adverse effects of magnesium deficiency on bone. *Growth Factors*. 2009 Dec;27(6):370-6. doi: 10.3109/08977190903152644. PMID: 19919525.
37. **Guerrero-Romero F, Rodríguez-Morán M**. Hypomagnesemia, oxidative stress, inflammation, and metabolic syndrome. *Diabetes Metab Res Rev*. 2006 Nov-Dec;22(6):471-6. doi: 10.1002/dmrr.644. PMID: 16598698.
38. **Garrison SR, Allan GM, Sekhon RK, Musini VM, Khan KM.** Magnesium for skeletal muscle cramps. *Cochrane Database Syst Rev*. 2012 Sep 12;2012(9): CD009402. doi: 10.1002/14651858.CD009402.pub2. Update in: *Cochrane Database Syst Rev*. 2020 Sep 21;9:CD009402. PMID: 22972143; PMCID: PMC7025716.

39. **Chen XY, Li J, Cheng WM, Jiang H, Xie XF, Hu R**. Effect of total flavonoids of Chrysanthemum indicum on the apoptosis of synoviocytes in joint of adjuvant arthritis rats. *Am J Chin Med*. 2008;36(4):695-704. doi: 10.1142/S0192415X08006168. PMID: 18711767.
40. **Cheon MS, Yoon T, Lee DY, Choi G, Moon BC, Lee AY, Choo BK, Kim HK.** Chrysanthemum indicum Linné extract inhibits the inflammatory response by suppressing NF-kappaB and MAPKs activation in lipopolysaccharide-induced RAW 264.7 macrophages. *J Ethnopharmacol*. 2009 Apr 21;122(3):473-7. doi: 10.1016/ j.jep.2009.01.034. Epub 2009 Feb 3. PMID: 19429315.