Review Article

AN OVERVIEW: ROLE OF PHYTOCHEMICALS IN THE PROPHYLAXIS OF MIGRAINE

Syeda Mah-E-Noor Zahra[1], Mahnoor Fatima[2], Babar Ahmad[3], Ibrahim Sohail[4]

Abstract

Migraine is one of the most painful and debilitating conditions encountered by 22.7% of people in Pakistan, thus many therapeutic strategies are being used to prevent and treat the symptoms and underlying pathology. The role of phytochemicals in the prevention of migraine attacks has been studied at different research centers around the world for many years. It has been found that intake of food as well as phytochemicals containing antioxidants such as flavonoids, polyphenols and alkaloids are involved in the reduction of migraine episode frequency. The current literature supports the use of these plant derived substances therefore if proven useful in other research including animal studies and human trials, can be given as an alternative or along with other prophylactic medical treatments so that better results can be yielded.

Key Words: Migraine, Headache, Serotonin, Vasodilation

doi: https://doi.org/10.51127/JAMDCV5I1RA01

How to cite this:
Zahra SMN, Fatima M, Ahmad B, Sohail I. An overview: Role of phytochemicals in the prophylaxis of migraine. JAMDC. 2023;5(1): 43-48
doi: https://doi.org/10.51127/JAMDCV5I1RA01

INTRODUCTION

The word "Migraine" is derived from "*Hemikrania*" a Greek word meaning 'pain in half of the head' as it is associated with a headache involving usually one side of the head.[1] It is considered a neurological as well as neurovascular disorder[2] and is characterized by recurrent headaches in which the pain is pulsating in nature[3], with moderate to severe intensity lasting from at least an hour to three days.[4]

The exact underlying mechanism is unknown but many theories exist regarding different factors involved in the pathophysiology of migraine and its signs and symptom.[5] Studies suggest that sensory nerves that surround blood vessels of the head and neck perceive pain when vasodilation occurs. The stretching of vascular smooth muscle along with pulsations from blood pumping cause the typical "throbbing" headache.[6]

Many systemic inflammatory diseases are linked with the predisposition of migraine attacks such as inflammatory bowel disease, multiple sclerosis and rheumatic diseases etc.[7-9] High cytokine levels in the blood indicate the presence of inflammation in the body during migraine episodes.[10,11] Studies support the involvement of other factors e.g., impaired cerebral glucose metabolism. Many studies link migraine attacks with low levels of the neurotransmitter serotonin and high levels of adenosine respectively.[12] Similarly, mitochondrial disability, where an imbalance occurs between the supply and demand of energy is also thought to be involved. The underlying oxidative stress may contribute towards disease susceptibility.[13,14]

One reason can be increased excitability in the cerebral cortex region and increased activity of pain neurons located in the trigeminal nucleus.[15] Another culprit involved is suggested to be Calcitonin Gene-Related Peptide (CGRP), a neuropeptide that

1Assisstant Professor Pharmacology, AMDC, Lahore.
[2-4]Demonstrator Pharmacology, AMDC, Lahore.

causes vasodilation thus leading to neurogenic inflammation.[16]

Genetics play a big role in the predisposition of migraine as the studies reveal most of the patients with migraine tendencies have a family history of migraine attacks.[17] Mental and physical stress are frequently related to migraine headaches.[18] Hunger, sleep disturbances, hypertension along with hormonal factors such as menstruation, menarche and menopause, use of oral contraceptive pills as well as pregnancy are also involved in the onset of pain.[19]

Studies show a correlation between migraine with certain diets such as foods containing tyramine and monosodium glutamate (MSG) therefore chocolates, cheese and alcoholic as well as carbonated drinks can be considered culprits behind the disease.[20] Environmental aspects such as bright lights, loud noises, smoke, humidity, sudden change in temperature or extreme weather are also thought to be linked with the triggering of attacks.[21]

The diagnosis of a migraine is mainly based on signs and symptoms.[22] Most of the people affected have an aura which is a transient period of visual disturbance indicating that the headache will occur soon. Headaches occur along with the feeling of heaviness and numbness in the upper limb and face on the same side.[23] Nausea and vomiting also occur as well as sensitivity to light, smell or sound.[24] If a migraine episode lasts longer than 3 days, it is termed "Status Migrainosus".[25] Other conditions like cluster headaches and meningitis can mimic the symptoms.[26]

Lifestyle modifications including a healthy diet and nutritional supplements significantly improve the symptoms of migraine. The incorporation of magnesium supplementation has shown positive results.[27] Alterations in behavior and habits such as healthy routines and smoking cessation greatly reduce the frequency of migraine attacks.[28] Acupuncture, massage and physiotherapy have been reported to help.[29]

If the condition persists, medication can be started such as beta-blockers, calcium channel blockers, angiotensin system inhibitors, antidepressants, anti-psychotics and anti-epileptic agents.[30] In an acute attack, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics or acetaminophen along with caffeine and aspirin are given for pain relief.[31] Antiemetics can also be given to subside the gastrointestinal effects.[32]

Triptans are the mainstay treatment of an acute attack of migraine.[33] The use of ergotamine is discouraged according to many researches.[34] In extreme cases, anesthetics can be given to combat the intense and resistant pain.[35] The main focus is to reduce the frequency in the first place thus prophylactic treatment is given to reduce not only the intensity of pain in upcoming migraine episodes but also to prevent the onset of attack to begin with.[36] But many adverse effects may be encountered with this drug.[37] Therefore, plant-derived substances studied that can be used as dietary supplements.[38]

DISCUSSION

Phytochemicals being alternatives to conventional therapy can be used for both acute and preventive treatment[39] as they have been reported to exert antioxidant effects. Their anti-inflammatory mechanisms and neuroprotective actions may also participate in their effectiveness.[40]

Correlation between dietary intake of phytochemicals containing active ingredients such as flavonoids and tannins etc. and prophylaxis of migraine has been established in many studies including recent researches.[41] Polyphenols one of them has shown to lower the severity of migraine by reducing oxidative stress.[42] A herb known as feverfew (*Tanacetum parthenium*) has also been reported to exert neuroprotective effects by inhibiting the release of serotonin from platelets and histamine.[43,44] Extracts of *Salix alba* showed a reduction in nitrite levels and neurotoxic stimuli induced serotonin turnover.[45] *Calotropis gigantea Linn*

expressed its effectiveness by interacting with dopamine and serotonin receptors whereas *Sargassum cristae folium* which contains alkaloids increases serotonin levels thus improving the symptoms of migraine.[46,47] Cannabinoids, containing terpene have analgesic and anti-inflammatory effects as suggested by researches.[48,49] Evidence regarding the benefits of Ginkgolide B in migraine prophylaxis is also present in different studies which suggest it to have glutamate modulatory and anti-platelet activity.[50]

CONCLUSION

The positive actions of these phytochemicals in the prophylaxis and treatment of migraine are supported by research data therefore detailed human trials can be conducted to determine the efficacy of the phytochemicals in migraine treatment especially prevention of acute attacks. Adverse effects can be assessed using animal models first. These thorough studies can be proven beneficial for patients especially in reducing the frequency and intensity of migraine episodes.

AUTHOR'S CONTRIBUTION

SMNZ: Conception of work, Acquisition of data and supervision
MF: Substantial contribution in design
BA: Drafting article reviewing of article
IS: Reference writing and reviewing of article

REFERENCES

1. Svitlana N. Words that started out as mistakes. Editorial board. 2021 Jan 19:576.. doi - 10.46299/ISG.2021.I.I
2. Sutherland HG, Albury CL, Griffiths LR. Advances in genetics of migraine. J Headache Pain. 2019 Dec;20(1):1-20. https://doi.org/10.1186/s10194-019-1017-9
3. Della Pietra A, Mikhailov N, Giniatullin R. The emerging role of mechanosensitive piezo channels in migraine pain. Int J Mol Sci. 2020 Jan 21;21(3):696.. https://doi.org/10.3390/ijms21030696
4. Peng KP, May A. Redefining migraine phases–a suggestion based on clinical, physiological, and functional imaging evidence. Cephalalgia. 2020 Jul;40(8):866-70. https://doi.org/10.1177/0333102419898868
5. Tanaka M, Török N, Vécsei L. Are 5-HT1 receptor agonists effective anti-migraine drugs?. Expert Opin Pharmacother. 2021 Jul 3;22(10):1221-5.. https://doi.org/10.1080/14656566.2021.1910235
6. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. Headache: J Head Face Pain. 2019 May;59(5):659-81. https://doi.org/10.1111/head.13529.
7. Welander NZ, Rukh G, Rask-Andersen M, Harder AV, International Headache Genetics Consortium, Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH. Migraine, inflammatory bowel disease and celiac disease: A Mendelian randomization study. Headache J Head Face Pain. 2023 Jan 27. https://doi.org/10.1111/head.14470
8. Moisset X, Giraud P, Dallel R. Migraine in multiple sclerosis and other chronic inflammatory diseases. Rev. Neurol. 2021 Sep 1;177(7):816-20. https://doi.org/10.1016/j.neurol.2021.07.005
9. Mathieu S, Couderc M, Pereira B, Dubost JJ, Malochet-Guinamand S, Tournadre A, Soubrier M, Moisset X. Prevalence of migraine and neuropathic pain in rheumatic diseases. J Clin Med.. 2020 Jun 17;9(6):1890. https://doi.org/10.3390/jcm9061890
10. Geng C, Yang Z, Xu P, Zhang H. Aberrations in peripheral inflammatory cytokine levels in migraine: A systematic review and meta-analysis. J Clin Neurosci. 2022 Apr 1;98:213-8.. https://doi.org/10.1016/j.jocn.2022.02.026
11. Thuraiaiyah J, Erritzøe-Jervild M, Al-Khazali HM, Schytz HW, Younis S. The role of cytokines in migraine: A systematic review. Cephalalgia. 2022 Dec;42(14):1565-88. https://doi.org/10.1177/03331024221118924
12. Petit JM, Eren-Koçak EM, Karatas HÜ, Magistretti P, Dalkara T. Brain glycogen metabolism: A possible link between sleep disturbances, headache and depression. Sleep Med Rev. 2021 Oct 1;59:101449. https://doi.org/10.1016/j.smrv.2021.101449
13. Bohra SK, Achar RR, Chidambaram SB, Pellegrino C, Laurin J, Masoodi M, Srinivasan A. Current perspectives on

mitochondrial dysfunction in migraine. Eur J Neurosci . 2022 Jul;56(1):3738-54. https://doi.org/10.1111/ejn.15676
14. Gross EC, Putananickal N, Orsini AL, Vogt DR, Sandor PS, Schoenen J, Fischer D. Mitochondrial function and oxidative stress markers in higher-frequency episodic migraine. Sci Rep. 2021 Feb 25;11(1):1-2. https://doi.org/10.1038/s41598-021-84102-2
15. Schulte LH, Peng KP. Current understanding of premonitory networks in migraine: a window to attack generation. Cephalalgia. 2019 Nov;39(13):1720-7. https://doi.org/10.1177/0333102419883375
16. Hanci F, Kilinc YB, Kilinc E, Turay S, Dilek M, Kabakus N. Plasma levels of vasoactive neuropeptides in pediatric patients with migraine during attack and attack-free periods. Cephalalgia. 2021 Feb;41(2):166-75. https://doi.org/10.1177/0333102420957588
17. de Boer I, van den Maagdenberg AM, Terwindt GM. Advance in genetics of migraine. Curr opin neurol. 2019 Jun;32(3):413.. doi: 10.1097/WCO.0000000000000687
18. Galvez-Sánchez CM, Montoro Aguilar CI. Migraine and neuroticism: A scoping review. Behav Sci. 2022 Jan 28;12(2):30. https://doi.org/10.3390/bs12020030
19. Dalateh Gomez L. Exogenous and Endogenous Female Sex Hormones Impact on Women with Migraine..
20. Gurria KI, Sharma S, Bhardwaj K. Wonders of phytomedicine in the management of neurological disorders. Eur J Mol Clin Med. 2020;7:2899-914.
21. Tymoszuk P. A New Approach to Headache and Migraine: Understand, manage and prevent your headaches. Pablo Tymoszuk; 2020 Jun 4.
22. Evans RW, Burch RC, Frishberg BM, Marmura MJ, Mechtler LL, Silberstein SD, Turner DP. Neuroimaging for migraine: the American Headache Society systematic review and evidence-based guideline. Headache: J Head Face Pain. 2020 Feb;60(2):318-36 https://doi.org/10.1111/head.13720..
23. Wilkinson F. Aura Mapping: Where Vision and Somatosensation Meet. Vision. 2021 Oct 30;5(4):52. https://doi.org/10.3390/vision5040052
24. Viera AJ, Antono B. Acute Headache in Adults: A Diagnostic Approach. Am Fam Physician . 2022 Sep;106(3):260-8.
25. Mehta D, Leary MC, Yacoub HA, El-Hunjul M, Kincaid H, Koss V, Wachter K, Malizia D, Glassman B, Castaldo JE. The effect of regional anesthetic sphenopalatine ganglion block on self-reported pain in patients with status migrainosus. Headache: J Head Face Pain. 2019 Jan;59(1):69-76. https://doi.org/10.1111/head.13390.
26. Al-Karagholi MA, Peng KP, Petersen AS, De Boer I, Terwindt GM, Ashina M. Debate: Are cluster headache and migraine distinct headache disorders?. J. Headache Pain. 2022 Dec;23(1):1-3. https://doi.org/10.1186/s10194-022-01504-x
27. Gazerani P. A bidirectional view of migraine and diet relationship. Neuropsychiatr. Dis. Treat.. 2021 Feb 11:435-51.
28. Raucci U, Boni A, Evangelisti M, Della Vecchia N, Velardi M, Ursitti F, Terrin G, Di Nardo G, Reale A, Villani A, Parisi P. Lifestyle modifications to help prevent headache at a developmental age. Front Neurol. 2021 Feb 2;11:618375. https://doi.org/10.3389/fneur.2020.618375
29. Ijaz N, Welsh S, Boon H. A mixed-methods survey of physiotherapists who practice acupuncture and dry needling in Ontario, Canada: practice characteristics, motivations, and professional outcomes. BMC Complement Altern Med. 2021 Dec;21(1):1-0. https://doi.org/10.1186/s12906-021-03440-w
30. Joshi S, Tepper SJ, Lucas S, Rasmussen S, Nelson R. A narrative review of the importance of pharmacokinetics and drug–drug interactions of preventive therapies in migraine management. Headache: J Head Face Pain. 2021 Jun;61(6):838-53. https://doi.org/10.1111/head.14135
31. Peck J, Urits I, Zeien J, Hoebee S, Mousa M, Alattar H, Kaye AD, Viswanath O. A comprehensive review of over-the-counter treatment for chronic migraine headaches. Curr Pain Headache Rep. 2020 May;24:1-9. https://doi.org/10.1007/s11916-020-00852-0
32. Orlova YY, Mehla S, Chua AL. Drug safety in episodic migraine management in adults part 1: acute treatments. Curr Pain Headache Rep. 2022 Jul;26(7):481-92. https://doi.org/10.1007/s11916-022-01057-3.

33. Yang CP, Liang CS, Chang CM, Yang CC, Shih PH, Yau YC, Tang KT, Wang SJ. Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. JAMA network open. 2021 Oct 1;4(10):e2128544-. doi:10.1001/jamanetworkopen.2021.28544
34. Aditya S, Rattan A. Advances in CGRP monoclonal antibodies as migraine therapy: A narrative review. Saudi J Med Med Sci. 2023 Jan 1;11(1):11. doi: 10.4103/sjmms.sjmms_95_22
35. Inan LE, Inan N, Unal-Artık HA, Atac C, Babaoglu G. Greater occipital nerve block in migraine prophylaxis: Narrative review. Cephalalgia. 2019 Jun;39(7):908-20..
36. Russo A, Silvestro M, Scotto di Clemente F, Trojsi F, Bisecco A, Bonavita S, Tessitore A, Tedeschi G. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience J Headache Pain. 2020 Dec;21(1):1-4.. https://doi.org/10.1186/s10194-020-01143-0
37. Ashina M, Buse DC, Ashina H, Pozo-Rosich P, Peres MF, Lee MJ, Terwindt GM, Singh RH, Tassorelli C, Do TP, Mitsikostas DD. Migraine: integrated approaches to clinical management and emerging treatments. The Lancet. 2021 Apr 17;397(10283):1505-18 https://doi.org/10.1016/S0140-6736(20)32342-4
38. Goschorska M, Gutowska I, Baranowska-Bosiacka I, Barczak K, Chlubek D. The use of antioxidants in the treatment of migraine. Antioxidants (Basel). 9 (2): 116..
39. Padayachee B, Baijnath H. An updated comprehensive review of the medicinal, phytochemical and pharmacological properties of Moringa oleifera. S Afr J Bot. 2020 Mar 1;129:304-16.. https://doi.org/10.1016/j.sajb.2019.08.021
40. Ferrante C. Pharma-toxicological and phytochemical investigations on Tanacetum parthenium and Salix alba extracts: Focus on potential application as anti-migraine agents..
41. Adam OM, Nugraha J, Hamdan M, Turchan A. Mechanism of the Bioactive Sargassum cristaefolium in Inhibiting Inflammatory Mediators in a Nitroglycerin-Induced Migraine Model in Rats. Pharmacogn J2022;14(2). doi:10.5530/pj.2022.14.50
42. Shojaei M, Sahebkar A, Khorvash F, Fallahpour S, Askari G, Bagherniya M. The effects of phytosomal curcumin supplementation on clinical symptoms, and inflammatory and oxidative stress biomarkers in patients with migraine: A protocol for a randomized double-blind placebo-controlled trial. Avicenna J Phytomed. 2023 Jan 1;13(1).
43. Vikelis M, Dermitzakis EV, Vlachos GS, Soldatos P, Spingos KC, Litsardopoulos P, Kararizou E, Argyriou AA. Open label prospective experience of supplementation with a fixed combination of magnesium, vitamin B2, feverfew, Andrographis paniculata and coenzyme Q10 for episodic migraine prophylaxis. J Clin Med.. 2020 Dec 27;10(1):67. https://doi.org/10.3390/jcm10010067
44. Tauchen J. Natural products and their (semi-) synthetic forms in the treatment of migraine: history and current status. Curr Med Chem. 2020 Jul 1;27(23):3784-808. https://doi.org/10.2174/0929867326666190125155947.
45. di Giacomo V, Ferrante C, Ronci M, Cataldi A, Di Valerio V, Rapino M, Recinella L, Chiavaroli A, Leone S, Vladimir-Knežević S, Kindl M. Multiple pharmacological and toxicological investigations on Tanacetum parthenium and Salix alba extracts: Focus on potential application as anti-migraine agents. Food Chem Toxicol. 2019 Nov 1;133:110783. https://doi.org/10.1016/j.fct.2019.110783.
46. Bhatia S, Al-Harrasi A, Kumar A, Behl T, Sehgal A, Singh S, Sharma N, Anwer MK, Kaushik D, Mittal V, Chigurupati S. Anti-migraine activity of freeze-dried latex obtained from Calotropis gigantea Linn. Environ Sci Pollut Res. 2021 Aug 19:1-9.. https://doi.org/10.1007/s11356-021-17810-x
47. Adam OM, Widjiati W. Role of Alkaloid on Platelet Aggregation and Serotonin in Migraine. Pharmacogn. J. 2022;14(3). doi:10.5530/pj.2022.14.81
48. Liktor-Busa E, Keresztes A, LaVigne J, Streicher JM, Largent-Milnes TM. Analgesic potential of terpenes derived from Cannabis sativa. Pharmacol Rev. 2021 Oct 1;73(4):1269-97 https://doi.org/10.1124/pharmrev.120.000046.
49. Graczyk M, Lewandowska AA, Melnyczok P, Zgliński A, Łukowicz M. Cannabinoids—

Perspectives for Individual Treatment in Selected Patients: Analysis of the Case Series. Biomedicines. 2022 Aug 2;10(8):1862. https://doi.org/10.3390/biomedicines10081862.

50. Barbalho SM, Direito R, Laurindo LF, Marton LT, Guiguer EL, Goulart RD, Tofano RJ, Carvalho AC, Flato UA, Capelluppi Tofano VA, Detregiachi CR. Ginkgo biloba in the aging process: A narrative review. Antioxidants. 2022 Mar 9;11(3):525. https://doi.org/10.3390/antiox11030525.