Herbal and Natural Compounds in Neuropharmacology: Biochemical innovations of Bio molecules used to manage Migraine

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Abstract

Migraine is a severe neurovascular condition that can significantly impair daily functioning, yet there are several targeted, well-tolerated, and effective treatment options available. The use of formulations derived from plant sources shows considerable potential in discovering new therapeutic targets for migraine management. Consequently, it is crucial to conduct safety and efficacy assessments. This review examines various phytomedicines that may aid in treating migraines, including feverfew, butterbur, menthol, ginger, ergotamine, caffeine, cannabis, curcumin, ginkgo biloba, serotonin, luteolin, glutamate, riboflavin, lavender and chamomile,focusing on their mechanisms of action and supporting evidence for treatment of migraine. This systematic review suggests that various herbal remedies, owing to their wide range of physiological effects, may serve as effective additions to migraine treatment. However, more rigorous, high-quality research is needed to evaluate their effectiveness and safety.

Key words: Migraine, Herbal treatment, Feverfew, Butterbur, Curcumin, Ginger, Anti-inflammatory, Analgesic activity, Chinese herbal medicine, Nutritional approach.

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1. Introduction

Migraine is a chronic condition that impacts approximately 20% of the population in India[1]. The Global Burden of Disease report by the World Health Organization ranks migraine as the third most common and sixth most disabling disease worldwide [2]. A significant percentage of people worldwide suffer from migraines, with women being more likely to get them (15%) than males (6%)[3]. Despite the availability of several effective medications for migraine prevention and treatment, there is growing awareness of medication overuse headaches, particularly associated with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids [4]. While medications can relieve symptoms during acute migraine attacks and help prevent future episodes—both important objectives—they do not offer a cure and often require long-term use [5]. Migraine is an intense headache often accompanied by sensitivity to light, sound, and head movement [6]. There are two main clinical subtypes of migraine: without aura and withaura. Classic migraine is accompanied with aura that contains some of the most identifiable neurologicaldisorder. In roughly 19–30% of migraine patients, symptoms such bright lights, scotomas, castles, neurological disturbances, and motor problems appear 20–40 minutes prior to headache. In addition to having migraine headaches, migraine without aura frequently causes phonophobia, photophobia, nausea, and vomiting, all of which can be made worse by exercise [7]. Recently, herbal supplements and nutraceuticals—such as feverfew, caffeine, menthol, curcumin, and serotonin—have been gaining popularity for migraine prevention. Their growing appeal is largely due to the perception of fewer side effects compared to conventional pharmacological treatments [8].

Fig. 1: Migraine

2. Materials and Methods

The study combines the various electronic databases from Google Scholar, PubMed Research Gate, Science direct and others.

3. Pathophysiology

The pathophysiology of migraine is complex and plays a significant role in determining how herbal treatments exert their effects [9]. The brain regions that are most important in reversing migraine pain are the cerebral cortex, thalamus, hypothalamus, and brain stem. The meninges themselves and their blood vessels, particularly the internal arteries, are where the migraine headache process starts in significant part. Current understanding indicates that neurogenic inflammation involving the trigeminal nerves and the inhibition of 5-HT1B/1D receptors are primary contributors to migraine headaches—contrary to earlier beliefs that vascular dilation was the initial trigger. Additionally, the trigeminal nerve transmits sensory information from the muscles and skin of the head to the central nervous system, playing a key role in the onset and progression of migraines. The trigeminal nerve also sends additional information from the head's muscles and skin to the central nervous system, which aids in the onset and progression of migraine. Various vasoactive neuropeptides—including serotonin, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide (PACAP), histamine, substance P, neurokinin A, bradykinin, and prostaglandins—play crucial roles in regulating neurogenic inflammation, platelet activation and aggregation, and mast cell degranulation associated with migraine[10]. Identifying and eliminating migraine triggers, when feasible, is essential for potentially resolving the condition without relying on medication or natural remedies. Common dietary triggers include vasoactive amines, tannins, salicylates, food additives, monosodium glutamate (MSG), caffeine, aspartame, nitrites, and alcohol[11]. Therefore, initiating an elimination-challenge diet at the earliest opportunity is crucial for accurately identifying potential food triggers in most patients. It's important to note that blood antibody tests for food sensitivities are not advised in this context. These tests often miss non-immune-related food reactions, leading to frequent false negatives. In fact, one of the most well-conducted randomized trials found that elimination diets based on serum antibody testing offered only

questionable and short-term benefits at best[12]. Additional potential triggers that may require attention include hormonal regulation, stress management, maintaining a regular and sufficient sleep pattern, and consistent meal timing, as fasting is a commonly reported migraine trigger. While patients work with their healthcare providers to identify and minimize these factors, herbal remedies may help provide symptomatic relief. These natural treatments can help soothe the neurovascular responses that lead to migraines, possibly aiding in the prevention of future attacks[13].

Mechanism

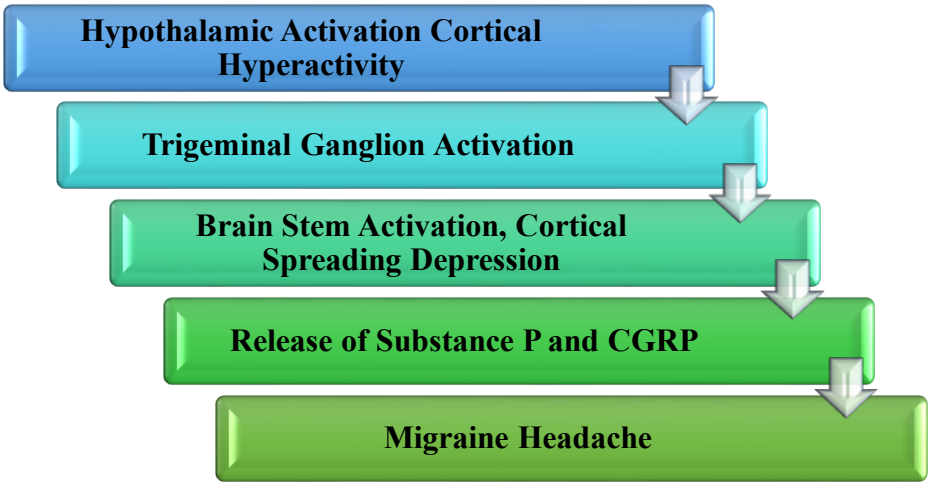


Fig 1: Causative factors of migraine

4. Use of herbals as alternative treatment for migraine

Nature has long served as a source of healing, with many modern medicines derived from natural substancesoften inspired by traditional medicinal practices. Increasingly, research supports the efficacy of several complementary and alternative therapies in the management of migraines. Among the most promising options for migraine relief areherbal remedies [14]. Numerous herbal remedies and formulations have proven effective for individuals suffering from migraines, offering both treatment and preventive benefits. Their effectiveness is often greater when combined with the identification and avoidance of migraine triggers [15]. Medicinal plants are a key component of human healthcare. Traditional medicine encompasses a broad spectrum of ancient natural healing systems, including Ayurveda, Siddha, and Unani are traditional systems of medicine that utilize herbal

remedies extensively. In recent years, the use of such herbal treatments has been steadily increasing in the Western world, with approximately 40% of individuals reporting their use within the past year [16]. The herbs used in management and treatment of migraine are detailed below.

4.1 Feverfew

Biological name: Tanacetum parthenium

Synonym: Chrysanthemum parthenium

Family: Asteraceae

Feverfew is commonly used as a preventive treatment for migraine headaches and is also employed in the management of arthritis [17]. Tanacetum parthenium L., a perennial plant from the Asteraceae (daisy) family, is commonly found in gardens and along roadsides in Europe's Balkan Mountains. It is spread to regions including Australia, China, Japan, and both North and South America[18]. Crude feverfew powder—more effectively than feverfew extracts or isolated parthenolidehas been shown to block the release of neuronal serotonin. In studies conducted on rats, the crude powder was also found to inhibit 5-HT2A/2B receptors. However, heat exposure significantly reduced this activity by degrading the parthenolide content in the extracts by more than 10% [19]. Studies have explored the effects of combining feverfew with other natural products, yielding mixed outcomes. In an open-label trial conducted in France with 12 migraine patients, a twice-daily combination of 300 mg feverfew and Salix alba (white willow) bark significantly reduced both the frequency and severity of migraine attacks compared to baseline levels [20]. However, a double-blind, randomized trial involving 49 American participants found that a combination of 100 mg feverfew, 400 mg riboflavin, and 300 mg magnesium did not demonstrate greater efficacy in reducing migraine frequency than a lower dose of riboflavin (25 mg) alone [21]. Notably, both studies reported that 42–44% of participants experienced at least a 50% reduction in migraine episodes.

4.2 Butterbur

Biological name: Petasites

Synonym: Butterfly-dock

Family: Asteraceae

Butterbur (*Petasites hybridus*), a member of the Asteraceae family native to Europe, is obtained from the rhizomes and stems of the perennial butterbur plant. Traditionally, butterbur extracts have been used in the treatment of various conditions, including asthma, gastrointestinal issues, respiratory disorders, and even cancer. Commercial preparations are usually derived from the root, rhizome (underground stem), or leaves of the butterbur plant. Although the precise mechanism of action remains unclear, butterbur is thought to influencecalcium channel regulation and inhibit the biosynthesis of peptide leukotrienes. These actions may help reduce the inflammatory responses associated with migraine attacks [22]. The primary active compounds in butterbur are sesquiterpenes, such as petasin and isopetasin. These compounds exhibit strong anti-inflammatory properties by inhibiting leukotriene synthesis and suppressing the release of prostaglandin E2 through COX-2 pathway modulation [23]. A meta-analysis of two randomized clinical trials found that an unsaturated pyrrolizidine alkaloid (uPA)-free butterbur extract, administered at a dose of 50 mg two to three times daily, significantly reduced the frequency of migraines compared to a placebo [24]. However, due to heterogeneity between the studies, the trial data could not be pooled for a unified analysis. The two trials included a total of 293 participants and were conducted over 12 to 16 weeks. Following the publication of this meta-analysis, a preliminary randomized, double-blind study was conducted involving 58 German children with migraines. This trial compared the effects of the same uPA-free butterbur extract, music therapy, and a placebo [25]. Only music therapy demonstrated a significant reduction in migraine attack frequency compared to the placebo, eight weeks following the 12-week treatment period. However, at six months post-treatment, both butterbur and music therapy were found to reduce migraine frequency compared to placebo [13].

4.3 Menthol

Biological name: Mentha arvensis

Synonym: peppermint camphor

Family: Lamiaceae

Menthol is a naturally occurring compound found in mint plants such as peppermint and spearmint. When applied to the skin or mucous membranes, it creates a cooling sensation by acting on nerve and smooth muscle fibres. Beyond its sensory effects, menthol has several pharmacological properties that may be beneficial in the context of migraine treatment [26]. Menthol exerts its analgesic effects by activating kappa opioid receptors and stimulating TRPM8 receptors, which are responsible for producing a cooling sensation [27]. Menthol also inhibits energy-dependent sodium channels, helping to reduce sensory input [28]. As a spasmolytic agent, it may alleviate tension in the peri cranial tissues and, by improving myofascial function, reduce cognitive symptoms associated with migraines, such as sensory intolerance[29]. Additionally, menthol may block the transmission of pain signals from blood vessels to the brain via the trigeminal nerve. Its anti-inflammatory properties, including the suppression of prostaglandin E2, leukotriene B4, and interleukin-1β, further support its role as a potential migraine-relieving agent [30].

4.4 Ginger

Biological name: Zingiber officinale

Synonym: Spirit

Family: Zingiberaceae

Ginger (*Zingiber officinale* Rosc.), a member of the Zingiberaceae family, it originated in Southeast Asia and has been grown for thousands of years in tropical and subtropical regions. It is widely used both as a culinary spice and for its medicinal properties [31]. Various mechanisms have been suggested to explain ginger's analgesic properties. A major pathway includes the suppression of arachidonic acid metabolism by cyclooxygenase (COX) enzymes, which is similar to the mode of action of non-steroidal anti-inflammatory drugs (NSAIDs) [32].

Additionally, ginger inhibits lipoxygenase (LOX), another enzyme involved in the arachidonic acid cascade [33]. Inhibiting both the COX and LOX pathways simultaneously may boost anti-inflammatory effects while reducing potential side effects [34]. Furthermore, shogaols—bioactive compounds found in ginger—appear to regulate neuroinflammation by downregulating inflammatory markers in microglial cells [35]. Gingerols, another class of compounds in ginger, may also activate vanilloid receptors, which are typically stimulated by capsaicin, contributing to pain relief [36]. Despite these promising mechanisms, clinical evidence remains limited, there is limited evidence supporting the use of ginger for migraine relief, consisting of only a few uncontrolled studies and a single case report [37].

4.5 Ergotamine

Biological name: Claviceps purpurea

Synonym: Rye ergot

Family: Clavicipitaceae

Claviceps purpurea—commonly referred to as ergot of rye, though it also affects wheat, triticale, and barley—is notable both as an ancient herbal remedy and as a major cause of disease. Over time, this genus of fungi has contributed to the development of an entire class of versatile and highly effective medications. These include naturally occurring alkaloids such as ergotamine and ergometrine (also known as ergonovine), This includes a range of synthetic derivatives such as methylergometrine (methylergonovine), dihydroergotamine, ergoloid mesylates, methysergide, cabergoline, pergolide, and bromocriptine. Historical records indicate that ergot of rye was identified as a grain contaminant as far back as 600 BCE [38]. A lack of understanding about ergot's toxicity led to recurring outbreaks of what was almost certainly ergotism, as suggested by historical descriptions that closely match the symptoms of the disease. During the Middle Ages, widespread epidemics were reported, characterized by symptoms including gangrene, nausea, vomiting, severe burning sensations in the limbs, convulsions, and hallucinations—frequently leading to death [39]. These outbreaks were worsened during times of

famine and war, when impoverished populations had no choice but to consume poor-quality rye contaminated with ergot. Although the connection between ergot and epidemic ergotism wasn't officially identified until 1630, such outbreaks continued to occur even afterward [40]. Ergot was first used to treat migraines in the 1800s, with early reports by Edward Woakes in 1868 and Albert Eulenburg in 1883. Ergotamine, isolated in 1918 by Arthur Stoll, became widely used for acute migraine treatment by 1926. It acts as a 5-HT1 receptor agonist, like triptans, but is less selective and more likely to cause side effects like nausea, vomiting, and dangerous vasoconstriction. Because of poor oral absorption, it's usually combined with caffeine and taken in forms like tablets or suppositories when migraine symptoms first appear. Although being potent and inexpensive, its side effects have restricted its application relative to triptans [41]. Evidence also suggests that long-term use of ergot derivatives may result in pleuropulmonary and retroperitoneal fibrosis [42]. These risks have played a significant role in the decreased use of ergot-based treatments for migraines [43].

4.6 Caffeine

Biological name: Coffea arabica

Synonym: Coffeine

Family: Methylxanthine

Caffeine, a naturally occurring methylxanthine, is likely the most widely consumed psychoactive substance globally. While it is most associated with coffee, it is also present in tea, chocolate, and energy drinks [44]. Long-term caffeine use in individuals with migraines can lead to several clinical outcomes. These include the worsening of existing headaches, withdrawal-related headaches (such as weekend migraines), and medication-overuse headaches from painkillers that contain caffeine. Interestingly, caffeine has a dual effect—it can both alleviate and trigger migraine attacks. Regular, habitual caffeine intake is linked to the occurrence of migraines and the development of chronic daily headaches.When consumed regularly, caffeine's stimulating properties and its ability to extend wakefulness may lead to sleep disturbances, which can, in turn, trigger migraine attacks through

this pathway. Because of caffeine's structural similarity to adenosine, research on adenosine's role in migraine development is particularly relevant. Studies have shown that blood levels of adenosine tend to rise during migraine attacks, and migraines or headaches are often reported following intravenous adenosine administration during heart-related treatments. In fact, IV adenosine has been documented as a migraine trigger in some cases [45]. A study involving migraine patients who consumed caffeine daily found that caffeine withdrawal significantly improved the effectiveness of triptan treatment. Seventy-two percent of those who stopped caffeine reported success, compared to only 40% in the group that continued caffeine use. The benefit was observed regardless of the amount of caffeine consumed before withdrawal. The results suggest that caffeine withdrawal can be beneficial in treating migraines, possibly due to the upregulation of adenosine receptors from chronic caffeine use, which may contribute to migraine attacks. However, caffeine withdrawal can also lead to rebound headaches due to vasodilation, which typically resolves within two weeks of abstinence [46]. Caffeine-containing pain medications are commonly used by headache sufferers, especially migraine patients, where caffeine acts as an adjuvant to enhance the effects of standard painkillers. Studies have shown that combinations of caffeine with paracetamol, acetaminophen, acetylsalicylic acid, and ibuprofen are significantly more effective in treating tension-type headaches (TTH) and migraines compared to their decaffeinated versions, with most patients tolerating them well. The most common side effects were nervousness, nausea, abdominal discomfort, and dizziness. A 130 mg caffeine dose boosts the effectiveness of analgesics for TTH, while 100 mg enhances their benefit for migraines [47] .

4.7 Cannabis

Biological name: Cannabissativa

Synonym: Marijuana

Family: Cannabaceae

Cannabis sativa, also referred to as marijuana or cannabis, is a historically significant plant from the Cannabaceae family, valued for its medicinal properties

and use as an entheogen. While it remains highly disputed, with a complex and often conflicting legal classification in many regions, it is gradually becoming more legalized. As research into its effects expands, migraine is likely to gain more attention as one of the conditions where cannabis may prove beneficial, considering its long-standing historical use [48]. Research into the use of cannabis for migraines has been constrained by legal and political barriers. Although its potential has been acknowledged in medical literature for years, no randomized, double-blind clinical trials have been conducted. Ironically, the absence of such studies is frequently used as justification to avoid initiating them, resulting in a classic 'catch-22' scenario [49]. A retrospective case study involving 121 adult migraine patients in Colorado, conducted following cannabis legalization, reported a reduction in migraine frequency of over 50% with the use of medical cannabis [50]. 40% of participants reported benefits, but only 12% said cannabis effectively halted an acute migraine episode. Drowsiness and challenges in controlling cannabis-related effects, likely due to variable doses, were the most common side effects. This study offers some support for cannabis as a potential migraine treatment but also emphasizes the need for more consistent and precise dosing methods. Interestingly, a 2007 a double-blind, randomized trial evaluating a THC inhaler for acute migraines was completed but its findings were never published, possibly indicating it was not effective [51]. Based on limited published studies and clinical observations, most patients report that inhaled cannabis is more effective than oral formulations for both treating and preventing migraines. For cannabis-naïve individuals, starting with low doses is recommended to minimize adverse effects—typically beginning with products containing 1 mg of THC and 1–2 mg of CBD per dose. Dosages can be gradually increased, either with each migraine episode (for acute relief) or weekly (for preventive use), until the desired effect is achieved or side effects become intolerable. Vaporizing crude, standardized cannabis extracts is preferred over smoking to reduce the risk of harmful effects on the lungs. This approach contrasts with using refined extracts found in some electronic cigarettes, which may contain potentially harmful additives [13].

4.8 Curcumin

Biological name: Curcuma longa

Synonym: Turmeric

Family: Zingiberaceae

Curcumin, the principal yellow pigment derived from turmeric (Curcuma longa), is the dominant curcuminoid found in the turmeric rhizome and ranks among the most well-known plant-based polyphenols [52]. Various studies have proposed mechanisms by which curcumin may offer neuroprotective effects. Renowned for its anti-inflammatory effects, curcumin modulates the expression of cytokines, chemokines, and various apoptotic factors [53]. It is recognized as a cytokine-modulating anti-inflammatory agent, It can suppress the activation of critical transcription factors, including NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), STAT (signal transducer and activator of transcription), and AP-1 (activator protein 1) [54]. Curcumin is particularly noted as a potential NF-κB inhibitor [55]. Additionally, it supports mitochondrial integrity and function, thereby preserving cellular and synaptic activity [56].

4.9 Ginkgo biloba

Biological name: Ginkgo biloba

Synonym: Ginkgo

Family: Ginkgoaceae

Ginkgo biloba leaves come from the Ginkgo biloba tree, a unique species within the Ginkgoaceae family. This ancient tree is the only surviving member of its family and has no close botanical relatives [57]. Ginkgolide B, a bioactive compound extracted from Ginkgo biloba leaves, functions as a natural modulator of glutamate signaling in the central nervous system (CNS) [58]. Additionally, Ginkgolide B functions as a potent anti-inflammatory agent by inhibiting platelet-activating factor (PAF), a powerful molecule involved in inflammation and pain signalling, which is released during inflammatory responses [59]. Platelet-activating factor (PAF), released by platelets and leukocytes in the early stages of a migraine attack, can

enhance trigeminovascular system activity and play a role in the development of migraine pain. Because of its ability to inhibit PAF, ginkgolide B—a compound from Ginkgo biloba—shows potential as a promising therapeutic option for treating migraine with aura [60].

4.10 Lavender

Biological name: Lavandulaangustifolia

Synonym: Lavanda

Family: Lamiaceae

Lavender, a perennial flowering plant belonging to the Lamiaceae family, is native to the western Mediterranean region [61]. It can grow up to 10 feet (3 meters) tall and is known for its purple-lilac blossoms [62]. Lavender, a member of the Lamiaceae family, has been used in traditional medicine for centuries. It boasts a wide range of applications and a rich history of medicinal use [63]. Numerous studies have explored the mechanisms behind lavender's effects on neuronal tissues. It has been shown to inhibit the inflammatory response triggered by lipopolysaccharides in human THP-1 monocyte cells, a process that may be linked to the expression of HSP70. Among various compounds tested, lavender demonstrated the weakest antioxidant and cholinergic inhibitory activity [64]. Linalool inhibits acetylcholine release and regulates ion channel activity associated with neuromuscular signaling [65].

4.11 Chamomile

Biological name: Matricariachamomilla

Synonym: Matricariarecutita

Family: Asteraceae

Matricaria chamomilla, also known as Matricaria recutita, is commonly referred to as chamomile (or camomile) and is alternatively known as German chamomile, Hungarian chamomile (kamilla), wild chamomile, blue chamomile, or fragrant mayweed. This annual herb belongs to the Asteraceae family [66]. Nitric oxide plays

a crucial role in the pathogenesis of migraine headaches. Preventing or reducing its activity may be beneficial in managing migraine attacks and associated pain [67]. Nitric oxide (NO) plays a crucial role in modulating moderate sensory sensitivity. As a result, inhibition of nitric oxide synthase (NOS) has become a potential focus for migraine therapy [68]. Hydrophilic compounds in chamomile—primarily polyphenols such as flavonoids, with apigenin as a major component—have been demonstrated to suppress the expression of nitric oxide synthase (NOS) in activated macrophages, thereby decreasing the production and release of nitric oxide (NO) [69]. This effect is also observed in chamomile essential oils, particularly due to compounds like chamazulene. These components can help reduce inflammation and alleviate migraine pain. Traditionally, chamomile has been used to treat inflammation, pain, neuralgia, and related conditions [70]. Additionally, sesame oil, which contains fatty acids and sesamin, was historically used on its own as a remedy for headaches [71]. Sesame oil has demonstrated anti-inflammatory effects when used externally to prevent chemically induced phlebitis [72]. When used alongside other therapeutic agents, sesame oil has demonstrated analgesic effects comparable to those of salicylate ointment in individuals with knee osteoarthritis [73]. Sesamin, a major bioactive component of sesame oil, possesses notable anti-inflammatory properties. Sesame oil is believed to function not only as a carrier but also as a potential aid in relieving pain during migraine attacks [74].

4.12 Serotonin

Biological name:5-hydroxytryptamine (5-HT)

Synonym: Hickory

Family: Juglandaceae

Serotonin (5-HT) has been implicated in the pathophysiology of migraines, initially observed through elevated urinary excretion of its metabolite, 5-HIAA, during migraine attacks. Although not all studies have replicated this finding, consistent patterns have emerged showing increased plasma 5-HT and decreased 5-HIAA levels during migraine episodes. Conversely, between attacks, patients often exhibit low plasma 5-HT and elevated 5-HIAA levels. These fluctuations are thought to

reflect dysfunctions not only in platelet activity but, more significantly, within the brain. This pattern supports the hypothesis that chronically low serotonin levels may predispose individuals to migraines, while abrupt surges in 5-HT may act as a trigger for attacks [75]. Recent research indicates that short-term depletion of brain serotonin (5-HT) through tryptophan reduction leads to symptoms such as nausea, dizziness, and motion sickness in healthy individuals, but not in those with migraines. However, in migraine patients, tryptophan depletion has been associated with increased headache severity, suggesting that impaired 5-HT synthesis and neurotransmission may worsen migraine symptoms. Furthermore, a recent neuroimaging study found elevated availability of brainstem serotonin transporters (5-HTT) in individuals with migraines, pointing to a dysregulation in the brainstem serotonergic system. This alteration may contribute to reduced synaptic 5-HT levels, potentially resulting from diminished synthesis or release, or from enhanced degradation of serotonin [76]. Physiological evidence strongly supports the association between migraines and reduced serotonergic activity. Migraine patients often exhibit increased intensity dependence of auditory and visual evoked potentials between attacks, indicating impaired serotonin (5-HT) transmission and altered sensory processing. This characteristic, linked to diminished cortical habituation, may stem from reduced reactivation of sensory cortices influenced by neurotransmitters in brainstem aminergic pathways. Additional support comes from studies showing that 5-HT1B/1D receptor agonists—which suppress serotonin synthesis—lead to increased amplitudes of auditory evoked potentials in both migraine sufferers and healthy subjects [77]. Immediately before and during a migraine attack, the cortical habituation deficit typically observed between attacks appears to normalize, suggesting a transient restoration of normal cortical excitability. This may be due to activation of brainstem aminergic nuclei that project to the cortex and thalamus. Evidence for increased serotonin (5-HT) involvement includes findings that drugs promoting 5-HT release or inhibiting its reuptake—such as fenfluramine, reserpine, and some SSRIs—can trigger migraine attacks more often in migraine sufferers. However, long-term use of some of these drugs may lead to resistance to migraines and administering 5-HT during an attack can relieve symptoms. These findings suggest that early-stage release of 5-HT from intracellular stores may play a key role in triggering migraines [78].

4.13 Luteolin

Biological name: Daucus carota subsp. Sativus (Carrot)

Synonym: Brainwash

Family: Apiaceae

Luteolin is a flavonoid, a plant-derived compound recognized for its potential health benefits. It is a yellow crystalline substance with a bitter taste and belongs to the polyphenol class of compounds [79]. Luteolin is present in a wide range of foods, including fruits, vegetables, herbs, teas, and nuts, with particularly high levels in celery, parsley, thyme, and peppers. It possesses antioxidant, anti-inflammatory, anticancer, anti-allergic, and neuroprotective properties [80]. Luteolin may promote skin health, support cardiovascular function, and reduce oxidative stress. Importantly, its ability to combat neuroinflammation suggests potential in managing migraines by protecting neurons, reducing inflammation, and modulating pro-inflammatory signalling pathways. Ongoing research highlights its promise in decreasing migraine intensity and frequency [81]. Incorporating luteolin-rich foods such as celery and parsley into a migraine-friendly diet may contribute to lowering the risk of migraine attacks. Although luteolin holds potential due to its anti-inflammatory and antioxidant properties, individual responses may differ, as migraine is a multifactorial condition with diverse triggers. This study aims to provide insight into luteolin's pharmacokinetics and toxicity, which could support future formulation development. Additionally, docking analysis will explore luteolin's binding affinity with CGRP proteins, offering further understanding of its potential role in migraine management [82].

4.14 Glutamate

Biological name: Uncaria tomentosa (Cats clove)

Synonym: Animal Nail

Family: Madder

Glutamate is a promising potential target for new migraine treatment research due to its critical role in brain functions, including pain modulation, nociceptive

sensitization, and its interactions with the opioid system and sensory signal transmission [83]. Glutamate excitotoxic pathways are thought to be the means through which mGluRs contribute to migraine mechanisms, [84] as they can lead to neuronal hyperexcitability and sustained pain, thereby intensifying migraines and promoting their chronification [85]. There is some, albeit inconsistent, evidence indicating elevated glutamate levels in plasma, saliva, and cerebrospinal fluid (CSF) in individuals with migraine, both during attacks and in interictal periods [86]. Additionally, it has been suggested that commonly used migraine preventive medications, even those without a direct glutamatergic mechanism, may reduce plasma glutamate levels [87]. Spectroscopy imaging studies suggest that glutamate levels may be elevated in certain brain regions, such as the occipital cortex, in people with migraine. However, findings are inconsistent. For example, while increased glutamate has been observed in adults, pediatric studies show decreased occipital glutamate during attacks. Visual snow syndrome, a condition linked to migraine, is associated with reduced glutamatergic connectivity in the anterior cingulate cortex. Overall, results on glutamate changes in migraine—across brain regions and populations—remain mixed and inconclusive [88].

4.15 Riboflavin

Biological name: Spinacia oleracea (Spinach)

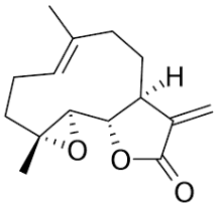
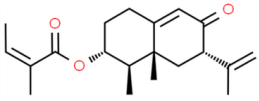
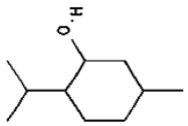
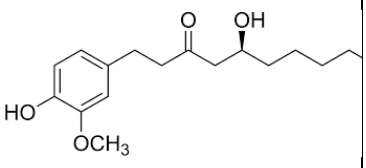
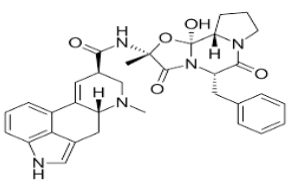
Synonym: Spinacia oleracea

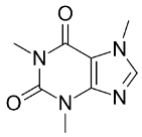
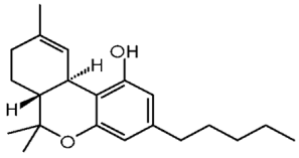
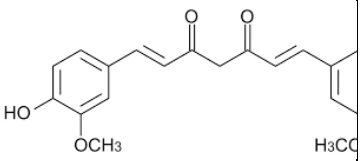
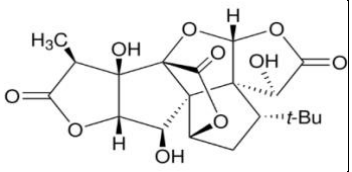
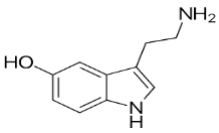
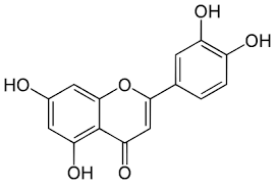
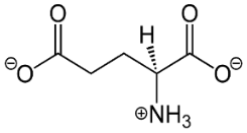
Family: Amaranthaceae

Riboflavin (vitamin B2) is a vital water-soluble nutrient that plays a key role in preventing a range of health conditions [89]. "Riboflavin has been extensively studied for its biological activities, including antioxidant, anti-aging, anti-inflammatory, and anti-nociceptive effects. Migraine pathophysiology is thought to involve oxidative stress linked to mitochondrial dysfunction, along with neuroinflammation driven by the glial cell network [90]. Riboflavin may relieve migraines through several mechanisms, notably by reducing oxidative stress and neuro-inflammation[91]. Riboflavin is heat-stable and not affected by cooking, but it can be destroyed by light. It is found in many foods, with dairy products and green leafy

vegetables serving as rich dietary sources offering moderate amounts. However, 10–15% of the global population has a genetic limitation in absorbing and utilizing riboflavin, leading to a potential risk of deficiency worldwide [92]. Riboflavin is administered to migraine sufferers because patients with mitochondrial encephalomyopathywho often experience migraine-like headaches—have shown relief from these headaches when treated with riboflavin. As a result, riboflavin has been employed as a preventive (prophylactic) therapy for migraines [93].

Biomolecules used in management of migraine:

Compound	Structure	Source	Uses	Reference
Feverfew (Parthenolide)		Tanacetum Parthenium (Feverfew plant)	Migraine prevention and reduce the severity of headaches	Bethesda, 2022 [94]
Butterbur (Petasin &Isopetasin)		Petasites hybridus (butterbur) plant	Prevention of migraine	Kulinowski Ł. et al. 2022 [95]
Menthol		Mentha piperita (peppermint plant)	Relieve migraine symptoms	Mikaili P. et al. 2013 [96]
Ginger(Gingerol)		Rhizome of ginger plant	Reduce migraine pain	Bethesda, 2024 [97]
Ergotamine		Fungus Claviceps purpurea	Treat or prevent migraine headaches	Tfelt-Hansen P. 2001 [98]

Caffeine		Leaves, seeds, and fruits of coffee beans, tea leaves, and cocoa beans	Analgesic adjuvant	Sawynok J. 1995 [99]
Cannabis		Flowering tops or buds of cannabis plant	Reduces migraine-associated nausea and vomiting following six months of use	Mahmood F. et al. 2022 [100]
Curcumin		Rhizome of the turmeric plant	Anti-inflammatory, analgesic and antioxidant properties	Slika L. et al. 2020 [101]
Ginkgolide B		Leaves and roots of Ginko biloba tree	Acute treatment of aura and anti-inflammatory	Hu H. et al. 2018 [102]
Serotonin		Synthesized from the essential amino acids	Onset and treatment of migraine	Jannini TB. et al. 2022 [103]
Luteolin		It is a flavonoid commonly found in a variety of fruits, vegetables, and herbs. E.g.: celery, carrots, peppermint.	Its anti-inflammatory and antioxidant properties may help reduce neuroinflammation	Aziz N. et al. 2018 [104]
Glutamate		Found naturally in various foods, both plant and animals	Prevention of migraine	Pearl NZ. et al. 2023 [105]

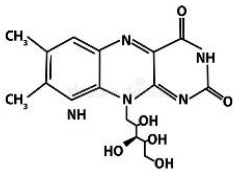
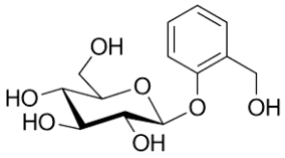
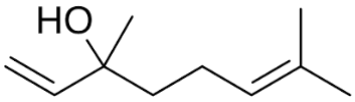
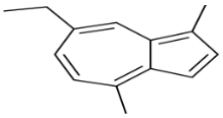
Riboflavin		Foods such as meat, fish, poultry, eggs, dairy products, green vegetables, mushrooms and almonds	Maintain energy stores used by your brain	Mahabadi N. et al. 2023 [106]
White willow bark (Salicin)		Bark of willow trees	Pain-relieving and anti-inflammatory properties	Bethesda, 2024 [107]
Lavender (Linalool)		Extracted from lavender	Reduce migraine symptoms	Bavarsad NH. et al. 2024 [108]
Chamomile (Chamazulene)		Chamazulene is primarily found in plants, most notably German chamomile	Help reduce migraine pain and inflammation	Dai YL. et al. 2022 [109]

Table 1.: Biomolecules extracted from herbs in management of migraine

5. Migraine trigger foods

Certain foods and food components can induce migraines either immediately or over time, with 12% to 60% of migraine sufferers indicating food as a trigger. Common offenders include alcohol, chocolate, caffeine, dairy, processed meats, citrus fruits, tomatoes, onions, nitrates, biogenic amines, MSG, aspartame, and sodium imbalances. Among these, caffeine withdrawal and MSG have the most robust evidence as migraine triggers. The effects differ by individual, amount of exposure, and timing. Research on avoiding trigger foods yields mixed findings, but clinical evidence suggests that recognizing and removing trigger foods—through observation, food journals, or elimination diets—can effectively lessen migraine frequency, duration, and severity for certain individuals [110].

6. Chinese Herbal Medicine on Migraine

Headache, a prevalent and debilitating condition globally, creates a considerable economic strain, with high rates in the U. S. , Europe, and China. Even though treatments such as triptans are available, their application is restricted due to factors like expense, contraindications, and side effects, resulting in a demand for alternative therapies. Traditional Chinese Medicine (TCM), with a particular emphasis on Chinese Herbal Medicine (CHM), has been utilized for alleviating headaches for an extended period, with herbs such as Rhizoma Ligustici Chuanxiong, Rhizoma Gastrodiae, and Baicalein exhibiting encouraging biological activities. While randomized controlled trials (RCTs) have examined the efficacy and safety of CHM, previous systematic reviews have been inconclusive because of inadequate study quality. This study intends to reevaluate CHM for headaches following stringent Cochrane review standards to present more robust evidence-based recommendations [111].

7. Precision Nutrition: A New Direction for Migraine Care

An extensive array of nutritional approaches has been investigated for migraine management, including nutritious diets, avoidance of trigger foods, weight loss strategies, ketogenic diets, gluten-free diets, and high-omega-3/low-omega-6 diets. Supplements like B vitamins, magnesium, CoQ10, omega-3s, and more have also been examined. However, the variety of choices complicates clinical implementation. A “precision nutrition” method—customizing dietary interventions according to clinical symptoms and biomarkers—may assist in directing treatment and future investigations. The review suggests a foundational, theoretical framework for structuring nutritional strategies, but it stays hypothetical and necessitates further confirmation prior to clinical application [112].

8. Discussion:

Migraine has been linked to mutations in genes encoding metabolic enzymes located in both mitochondrial and nuclear DNA. The neurological and vascular disturbances associated with migraine may stem from impaired oxygen metabolism, driven by mitochondrial dysfunction, oxidative stress, and

inflammation—factors that influence vascular tone [113]. Migraine is also associated with various comorbid conditions, including cardiovascular disease, stroke, asthma, epilepsy, allergies, and sleep disturbances [114]. Common triggers comprise fasting, skipped meals, stress, and inadequate sleep [115] .

Migraine is linked to elevated cortical excitability, with the trigeminal ganglion believed to play a key role in this heightened activity [116]. Stimulation of trigeminal sensory nerve fibers activates the brainstem and triggers the release of vasoactive peptides, such as substance P and calcitonin gene-related peptide (CGRP). This cascade leads to the activation of platelets and endothelial cells, promoting nitric oxide production, vasodilation, vascular permeability, and mast cell degranulation [117]. These events further stimulate trigeminal sensory fibers, leading to increased release of substance P and CGRP, and amplifying the transmission of pain signals across the brain [118].

Migraine is thought to result from disturbances in brain homeostasis, involving both genetic and neurovascular factors, though its exact pathophysiology remains incompletely understood. Familial forms of migraine have been linked to mutations on chromosome 19, with approximately 50% of cases associated with alterations in the CACNA1A gene, which encodes the Cav2.1 (P/Q-type) voltage-gated calcium channel [119]. One possible consequence of this mutation is enhanced glutamate release. Mutations in the ATP1A2 gene, which account for approximately 20% of familial migraine cases, affect the Na^+/K^+ ATPase enzyme. These mutations reduce the efficiency of astrocytic glutamate transporters, leading to excessive glutamate accumulation at synapses—a factor believed to contribute to the onset of migraine headaches[120].

Migraine with aura is characterized by sensory, visual, or motor disturbances, including heightened sensitivity to light or sound, visual phenomena like zig-zag patterns, and sensations of numbness or tingling in the face or hands. This form of migraine impacts roughly 30% of patients. The aura is believed to be caused by a slowly moving wave of cortical depolarization, which activates the trigeminovascular system, nociceptors in cerebral blood vessels, and brain areas involved in pain perception and neurological symptoms [121].

9. Conclusion

Herbal medicines show promise in preventing and treating migraines. Feverfew has strong evidence for prevention, while curcumin, especially combined with omega-3 fatty acids or CoQ10, also shows potential. Herbal remedies such as menthol, peppermint oil, butterbur, coriander, Ginkgo biloba, ginger, lavender, and chamomile have shown potential benefits in migraine management, although further research is warranted. For mild migraine episodes, options like ginger, cannabis, intranasal cayenne, or Spanish lavender oil may be considered—particularly for individuals seeking to avoid pharmaceutical interventions. Preventive strategies may include herbs such as butterbur, turmeric combined with fish oil, goshuyuto, citron, and the Rectify Heaven Formula. While feverfew, ginkgo, and bushy mat grass have shown some promise, their supporting evidence remains limited. In more severe cases, natural therapies can serve as complementary approaches alongside pharmaceuticals, providing safer and more affordable alternatives when conventional treatments prove inadequate.

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