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Herbal drugs used for the treatment of migraine

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Abstract

From the ancient times the herbal drugs are being used widely for various medication purposes and to treat various diseases and disorders. In modern times the herbal drugs are given first preference for any kind of medication, as they have very less or no side effects. Similarly, for migraine the herbal remedies can provide a better option for the treatment. Herbal products are promising ways to treat migraine headache in migraine patients. So, in this work we will study about the various herbal therapies that are effective for the prophylaxis of migraine. The chemical constituents present in *Tanacetum Parthenium*, *Petasites hybridus*, Ginkgo biloba, Ginger and Peppermint have shown efficacious results in clinical studies. Hence, in this study our main focus will be on a detailed understanding of the herbal remedies for migraine, we will be mainly focusing on their source, family, chemical constituents, their dosage forms and mode of action.

Keywords: Preference, prophylaxis, *Tanacetum parthenium*, *Petasites hybridus*, ginkgo, ginger, migraine

Introduction

Migraine is the most frequently seen neurological problem in primary health care. According to the Global Burden Disease study, migraine is the second largest cause of world's disability, and is first cause among young women (Steiner *et al.*, 2020) [1]. Migraine is persistent disorder as it affects 18% of women and 6% of men worldwide, whereas chronic migraine affects 2% of the global population (Goadsby *et al.*, 2017) [2]. Migraine is basically chronic headache disorder categorized by recurrent attacks lasting for 4-72 hours, basically of moderate to severe intensity provoked by routine physical activity, generally associated with nausea, photophobia, vomiting (Gordon *et al.*, 2015) [3].

Types of Migraine

Migraine is basically a complex neurological disorder, that demonstrate various forms, each form presents distinct clinical characteristics.

- **Migraine with aura:** It involves short-term neurological symptoms like headache, visual disturbances. In comparison, migraine without aura is followed by pulsating headaches accompanied by symptoms like nausea and sensitivity to light and sound.
- **Chronic migraine:** Chronic migraine generally poses a remarkable health burden, followed by headaches that usually occurs on 15 or more than 15 days per month.
- **Menstrual migraines:** This type of migraine usually occur during menstrual cycle in females.
- **Vestibular migraines:** This type of migraine generally interferes with vestibular reflexes, this in turn causes symptoms like dizziness and balance disturbances.
- **Hemiplegic migraines:** This type is rare, characterized by temporary paralysis.
- **Retinal migraines:** Retinal migraines involve temporary vision loss in one eye (Charles *et al.*, 2018) [5].

Triggers for migraine

A migraine trigger can be any environmental, dietary or physiologic factor that can evoke migraine activity in the brain (Misra *et al.*, 2010) [6]. It is essential to have sufficient information or knowledge about the triggers for the proper management of the patients.

Pathophysiology

- **Environmental triggers:** Odours, bright light, noise. Painful stimuli that trigger migraine basically occurs in the head and neck. The most common of them are neck injury, spasm etc. 40% of people who are suffering from migraine report that they are affected by weather changes.
- **Food triggers:** Food products that are obtained by aging are found in fermented products like wine, aged cheese, yeast, fresh bread and yogurt. Foods that are similar to neurotransmitters for example coffee, chocolate etc.
- **Psychological triggers:** Stress, lack of sleep or alteration in sleep schedule, fatigue, hormonal changes.

To understand the pathophysiology of migraine the following theories were proposed.

a) Neurogenic and Vascular theories

The main cause of migraine headaches is still not completely recognized. Previously, two theories explaining the etiology of migraine headaches were proposed. The neurogenic theory basically focuses on the cause of migraine pain and is generally linked to trigeminovascular system. Whereas the vascular theory was introduced by Thomas Willis, he discovered out that “all the pain is an action violated” and proposed that the headache is caused by vasodilation of cerebral and meningeal arteries (Gooriah *et al.*, 2015) [8].

b) Cortical spreading depression

This theory suggests that cortical spreading depression is a wave of neuronal hyperactivity, chased by an area of cortical depression. The headache depends on activation of the trigeminovascular pain pathway.

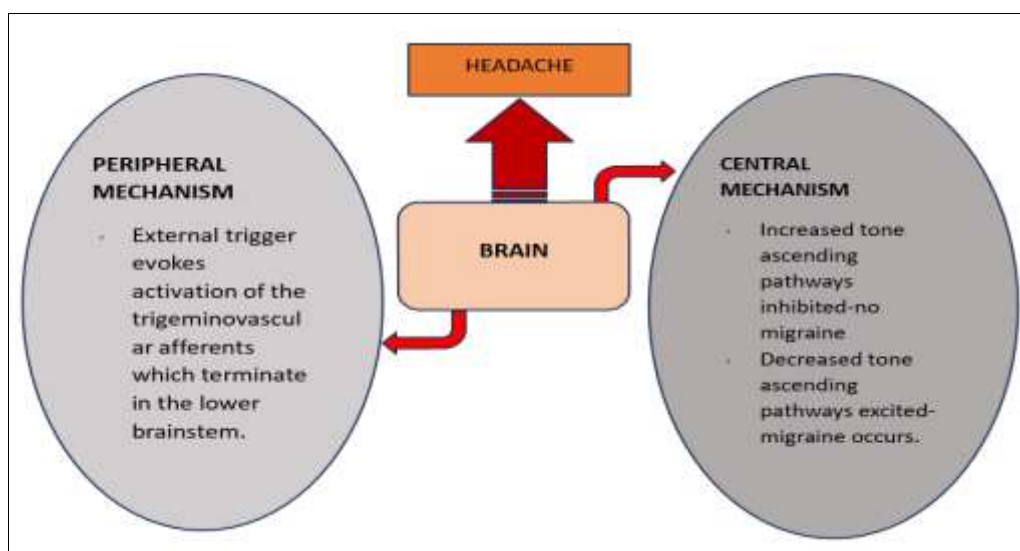


Fig 1: Pathophysiology of migraine

Modifications in lifestyle for migraine

Potential lifestyles that may be contributing for the headaches are essential to be discussed to understand how these can be managed and modified in order to prevent further progression of migraine.

Hydration: In an experiment, when random sample of children and adolescents aged 6-18 years, 56% of them were found to be mildly dehydrated on the basis of urine concentrations (Kenney *et al.*, 2015) [13]. Increasing water intake has been shown to improve headache severity in adults with headache. (Spigt *et al.*, 2012) [14]. It's said that fasting can provoke migraine (Drescher *et al.*, 2010) [15]. So, one must carry a water bottle with him or her and should stay hydrated.

Sleep: An improper sleep schedule can increase the severity of migraine and may also increase the frequency of headaches. Hence, the most important step in migraine prevention is the proper management of lifestyle. A consistent sleep schedule is must for the easy prevention of migraine. (Carissimi *et al.*, 2016) [12].

Physical activity: Regular physical activity is important for keep one's mind and body healthy and active. In a study, conducted on adults, aerobic exercise of 30 minutes three to four times a week was found to improve the frequency and

severity of migraine attacks similarly as efficacious as some preventive medications.

Diagnosis

Diagnosis of migraine can be done by the help of orthopaedic tests, cranial nerve examination, complete blood count, cranial magnetic resonance imaging, urinalysis can be performed if essential (Martin *et al.*, 2015) [20]. The International Classification of Headache Disorders defines the migraine by following criteria (Munoz *et al.*, 2019) [21].

- a) At least five attacks with headache lasting 4-72 hours. With 1 fulfilling criterion (c)-(d)
- b) Headaches having at least two of the following characteristics:
 1. Pulsating quality
 2. Unilateral location
 3. Worsening by physical activity, walking.
- c) During headache at least one of the following:
 1. Nausea and/or vomiting
 2. Phonophobia or photophobia

Herbal remedies for migraine

Herbal remedies that are used for migraine are basically obtained from the natural resources. They may be made from different parts of a plant. These are:

- Flowers
- Oil
- Roots

- Seeds
- Leaves
- Fruits

The herbal supplements are also available in different formulations such as:

- Liquids
- Tinctures
- Pills

Herbal drugs may be another option for migraine headaches, but before trying them it's important to consult a doctor. Some of the herbal drugs used to treat migraine are-

Feverfew: A Migraine remedy



Fig 2: Feverfew plant

Feverfew is basically a flowering plant, usually it bears white flowers.

Biological source: It is obtained from the flowering plant of '*Tanacetum parthenium*'.

Family: Asteraceae

The name of feverfew comes from the Latin word "febrifugia", which means "fever reducer". Traditionally it was used for treating fevers and other inflammatory conditions. In the modern times the use of feverfew has extended to the treatment of migraine, dizziness, inflammation and breathing problems. (Duke *et al.*, 1985) [23].

Dosage and safety measures for Feverfew

Dosage	100-200 mg daily
Frequency	Taken in one or two doses.
Precautions	Take professional advice before use, especially if pregnant or breastfeeding.

Side effects of Feverfew: Common side effects are stomach upset, diarrhoea and skin rash. Some individuals may have

Morphology

Colour: Flowers of feverfew are basically white in colour

Odour: Strong fragrance

The stems of plant are ribbed, it is usually woody at the base.

Shape and size: The size of flowers is about 1.5-2 cm.; the length of the plant is about 30-70 cm tall and having leaves of size about 8 cm in length (Fredrik *et al.*, 2023) [45].

Chemical constituents

Parthenolides: They are the potent anti-inflammatory compound that may reduce nerve inflammation.

Sesquiterpene lactones: They generally inhibit the production of chemicals that triggers migraines.

Flavonoids: Flavonoids are responsible for protection against oxidative stress and reduce stress. (Jackson *et al.*, 1986) [24].

Cultivation and collection of Feverfew

The plant can be cultivated in loamy, nutrient rich soil having moderate moisture. The crop basically requires a neutral pH, it efficiently grows well in hot climate. The seeds are sown in the month of march. The seeds are placed on the soil and are lightly pressed. With thorough watering the seeds germinate after 2-3 weeks. The plant gets matured in the month of June to October until the flowers are fully opened. The flowers are clipped off below the flowerheads with fingers or garden shears. Feverfew is available in variety of forms such as: Fresh, freeze dried, dried and also in supplement forms including capsule, tablet or liquid extract (Fredrik *et al.*, 2023) [45].

Modes of action of Feverfew

Reduce inflammation: Feverfew may block the release of inflammatory chemicals.

Inhibition of serotonin release: Serotonin is a neurotransmitter usually responsible for migraine triggers.

Blocking of pain signals: It interferes with pain signals that are sent to brain.

allergic reactions to it.

Butterbur: Inflammation and pain reducer.**Fig 3:** Butterbur plant

Biological source: Butterbur is basically derived from the leaves of the plant '*Petasites hybridus*'.

Family: Asteraceae

Butterbur is generally an herbal supplement that is effective in prophylaxis of adult migraines. The American Academy of Neurology 2012 and the American Headache Society indicated that butterbur is effective for migraine prevention and is a valid option for patients suffering from migraine to reduce the both severity and frequency of it (Holland *et al.*, 2012) [25].

In similarity to adult migraines, the *Petasites* is evidenced for the prevention of the paediatric migraines. (Orr *et al.*, 2018) [28]. In a random controlled trial in 2005, butterbur reduced the frequency of attacks by 50% in 77% of the paediatric experimental group (Malone *et al.*, 2018) [26].

Chemical constituents

Petasin and Isopetasin: These two chemical constituents are responsible for inhibiting leukotriene synthesis and inflammation. They are found in the extract of rhizomes and leaves of *Petasites*.

Essential oils**Pyrrolizidine alkaloids****Cultivation and collection of Butterbur**

Butterbur is generally planted in the spring season usually in the months from March to May. The habitats required for the planting butterbur are ditches, grasslands, meadows, streams etc.

The plant usually requires humid climate. The temperature required for optimum growth is 20- 300 C. The altitude required is 1200m above the sea level. The soil requirement is well drained, sandy loamy soil. The land should be ploughed 4-5 times. The spacing is 30cm x 30cm under bed system. The manures and fertilizers used should be rich in nitrogen, potassium and phosphorus. The crop can be harvested in about 8-9 months after sowing usually in the month of December. When the plant gets matured the leaves are close to the ground. (Gaertn *et al.*, 2023) [50].

Mechanism of action of Butterbur for the treatment of migraine.

Petasites is generally responsible for the inhibition of the opening of L-type voltage gated calcium ion channels, this

leads to a decrease in the vasoconstriction of vessels and excitation of the neurons (Orr *et al.*, 2018) [28]. The active components of the herb include sesquiterpenes (Petasin and Isopetasin) which exhibit the anti-inflammatory activity by the inhibition of COX- 2 enzyme. Thus, leading a decrease in leukotriene synthesis and prostaglandin E2 release.

Ginger: for treatment of migraine.**Fig 4:** Ginger

Biological source: It is obtained from the rhizome of the plant '*Zingiber officinale*'.

Family: Zingiberaceae

Ginger is basically obtained from the underground stem i.e. rhizome, it is widely used as spice in cooking. Ginger is grown in many parts of the world and has long been used as traditional medicine.

Chemical constituents

- Phenolic compounds
- Terpenes
- Polysaccharides
- Lipids
- Organic acids

Ginger has been recommended as an efficacious home remedy for the treatment of migraine as an acute treatment, it relieves both headache and associated nausea. "Ginger juice", is an effective recipe in which half a tablespoon of ground ginger is stir into a glass of water and can be taken as herbal tea, another method is to drink a hot tea made by a tablespoon of freshly ground ginger.

Ginger has shown potential analgesic efficacy, 500 to 600 mg of ginger powder when taken with water for at least two to three times a day is reported to be efficacious against migraine without any serious side effects (Mustafa *et al.*, 1990) [30].

Cultivation and collection

The soil requirement for ginger is deep, well drained, loamy, and humus rich in nature. The soil is prepared in the summers usually in March to April, and the land is ploughed twice. The crop is cultivated in the soil beds that are 1m wide, 3-6 m long and 15cm tall with a 30 cm gap between each bed. The climate requirement is warm and humid, the annual rainfall for optimal growth is 125-250 cm. The plot is cleaned by hand weeding during first 3-5 weeks. The crop is harvested

when the leaves turn yellow, usually after 8-10 months of plantation. A well grown crop gives an average yield of 20t/ha. In post harvesting the outer skin of is peeled and then dried under the sun for a week. For storage, rhizomes are treated with solution of Carbendazim + Mancozeb at 40gm/10 litre of water for 25 minutes, it prevents the rotting of rhizomes.

(Germplasm Resources Information Network, 2017) Mode of action of ginger

The analgesic activity of ginger is due to the chemical constituents present in it, these chemical constituents are gingerols and shogaols, they generally inhibit the prostaglandin biosynthesis by leading a decrease in the expression of the cyclooxygenase-2 enzyme (COX-2) (Jolad *et al.*, 2004) [31]. Ginger shows the anti-emetic properties and relieve nausea and vomiting was confirmed in patients with migraine (Marx *et al.*, 2002) [32].

Ginkgo biloba: as a prophylaxis for migraine.



Fig 5: Ginkgo biloba

Biological source: It is obtained from leaves of the plant 'Ginkgo biloba'.

Family: Ginkgoaceae

Ginkgolide B is the main chemical constituent responsible for the activity of ginkgo. Ginkgolide B has a vital role for the migraine prophylaxis.

Chemical constituents

- Terpenoids: The major terpenoids present in ginkgo are bilobalides (sesquiterpene) and ginkgolides (diterpenes). Bilobalides and ginkgolides are constituted in the all parts of the ginkgo seeds and the highest terpenoid content is obtained from the embryo and endosperm. (Han *et al.*, 2021) [34].
- Lignins: Lignans and their isomers are isolated from the shells surrounding the seeds.
- Proanthocyanidins: these are highly active, functional polyphenolic compounds. (Jiang *et al.*, 2020, Kulic *et al.*, 2022) [35, 36].
- Alkylphenols and Alkyl phenolic acids
- Polysaccharides

Cultivation and collection of Ginkgo biloba

The crop of ginkgo is basically cultivated by seed as well as stem cutting type of propagation.

sSeed propagation: the seeds are stored in an incubator at 50 C for three months. The seeds are dipped in water for 5-6 minutes, the seeds are then cleaned with a towel and are again incubated at 50 C, this process is followed after every 15 days of interval. Before sowing the humidity of 70% is maintained. A fine layer of sand is spread deep under the surface of soil beds. The seeds are then sown above this layer, a secondary layer of sand is spread over the top of the seeds. Irrigation is required whenever required.

Propagation through stem cuttings: It is done by using stem cuttings that are semi hard and are 3-4 years old, mainly thick as pencil. The stem cuttings are treated with selected growth hormones, they are usually planted in the month of December. The sprouting is observed in the month of April. The sprouted cuttings are placed in the greenhouse for three years under controlled conditions at a temperature of 25 ± 20 C and a humidity of 70%. After 4 years they are shifted into polyethene sleeves. After 5 years these plants are ready to transfer in the field.

Generally, the pollination in the plant occurs in the month of August to late September. The matured seed of ginkgo consists of an encircled embryo which bears a soft, fleshy outer layer called sarcotesta. (Govaerts *et al.*, 2013) [48].

Harvesting and yield: The plant is harvested in the month of October to mid of November. The leaves are plucked manually, and are then dried under partial shade for a week.

Mode of action of Ginkgo biloba in prevention of migraine

It involves the modulation of the glutamatergic transmission in the CNS and antagonism of the platelet activating factor (PAF) receptor (Williams *et al.*, 2004) [38]. PAF plays its role as a proinflammatory and nociceptive agent released during inflammatory response. (Akisu *et al.*, 1998) [39].

Peppermint (Mentha piperita)



Fig 6: Mentha piperita

Peppermint is basically a fragrant herb obtained from the leaves of peppermint plant. It is most commonly used as teas, essential oils, and remedies, which provides numerous health benefits. In a recent study the effects of intranasal lidocaine 4% and peppermint essential oil drop of 1.5% concentrations were compared by performing tests 120 adult patients. After the administration of the treatments, the reports show the symptoms at different time intervals. While the researchers found a significant difference among the treatment groups in relation to reduction in intensity of headache. Particularly, in

the peppermint oil and lidocaine groups 40% of the patients experienced decrease in headache intensity. Especially 42% of the patients in the peppermint oil group responded efficiently to the treatment (Rafieian-kopaei *et al.*, 2019) [41].

Biological source: It is obtained from the leaves of the plant '*Mentha piperita*'.

Family: Lamiaceae

Chemical constituents

Volatile components: Menthol (33-60%), menthone (15-32%), isomenthone (2-8%), menthyl acetate (2-11%), β -caryophyllene (2-4%) and carvone (1%). (Clark *et al.*, 1981) [42].

Cultivation and collection of Peppermint

The seeds are sown in a nutrient rich soil basically black and red soils in the early spring season, usually soils with acidic pH. Temperature requirement for the crop is about 22-25°C. The seeds are planted at a depth of ¼ inch with 18-24 inches between seeds and a distance of 24 inches between the rows. The water requirement for optimal growth is 1 inch per week. The best time for harvesting the crop is when the flowers bloom. The stems are cut about an inch above the soil. The leaves are sun dried and are stored for further use. (Frampton *et al.*, 2011) [47].

Mode of action of *Mentha piperita* in migraine

Peppermint has a cooling effect which generally inhibits the muscle contractions in the neck and the head region and also stimulate the blood flow to the area. This cooling sensation comes from the volatile component present in the plant extract i.e. menthol. Menthol is also present in over-the-counter topical pain-relieving medications. Peppermint oil mainly has anti-inflammatory, analgesic, anti-infectious, antimicrobial, antifungal, vasoconstrictor, decongestant and stomachic properties. In case of migraine when the oil is applied around the head region, it shows a relieving action in reducing the pain. (Tassou *et al.*, 1995; Ravid *et al.*, 1994) [43, 44].

Turmeric: An effective remedy



Fig 7: Turmeric

Turmeric is basically a flowering plant from the ginger family. It is usually a perennial herb native to the Indian

subcontinent and southeast of Asia. The rhizomes of the plant are medicinally active and are used for the wide range of therapeutic usages. The rhizomes are used fresh, boiled with water or dried; the further process involves grinding them into fine powder. Finally, a deep orange-yellow powder is obtained which is commonly used as a colouring agent and flavouring agent.

Biological source: It is obtained from the rhizomes of the plant '*Curcuma longa*'.

Family: Zingiberaceae

Chemical constituents

- **Curcuminoids:** Curcumin is the primary curcuminoid responsible for bright yellow chemical produced by the plant which is approved by World Health Organisation. Other curcuminoids are: desmethoxycurcumin, bisdemethoxycurcumin, and curcumin diferuloylmethane. Curcuminoids are natural antioxidants and usually inhibit the compounds that induce inflammation (Yuan *et al.*, 2011).
- **Volatile oils:** Turmerone, atlantone and zingiberone.
- **Sugars**
- **Proteins.**

Cultivation and collection

The crop is cultivated with the help of rhizomes, basically planted by keeping the nodules facing upwards, planted in spring season. The altitude required for the crop is 1500m above the sea level. The crop can be planted in April-March. Irrigation is required according to the climate and soil. Manures like animal dung can be used for a good crop. Harvesting is done in months usually from January to April, the crop gets matured in 7-8 months. When the leaves turn yellow and start drying, it means the crop is ready for the harvest. The land is ploughed well and rhizomes are collected by handpicking or with spade clumps. Before curing, mother and finger rhizomes are separated. (Nair *et al.*, 2013) [49].

Mode of action of Curcumin in migraine

Turmeric is a natural detoxifier, pain reliever and anti-inflammatory agent. The main mode of action is still unknown but hypothetically, it acts mainly by inhibiting the inflammation and reducing the pain. The turmeric tea can be prepared by adding a tablespoon full of curcumin powder in a cup of hot water or milk.

Discussion

Since chronic migraine affects 2% of the world's population, migraine is a persistent condition that affects 18% of women and 6% of men globally. In essence, migraine is a chronic headache illness defined by recurrent episodes that last between four and seventy-two hours. The attacks are normally moderate to severe in intensity, brought on by regular physical activity, and they are typically accompanied by nausea, photophobia, and vomiting. Any dietary, physiological, or environmental element that can cause migraine activity in the brain can be considered a trigger for migraines. The following lifestyle choices could be causing your headaches: staying hydrated, getting enough sleep, and exercising. Orthopaedic testing, cranial nerve examinations, complete blood counts, cranial magnetic resonance imaging, and, if necessary, urinalysis can all be used to diagnose migraines. The natural resources are essentially where herbal

cures for migraines come from. They could be fashioned from various plant parts. These include: Fruits, Leaves, Flowers, Oil, Roots, and Seeds. Additionally, the herbal supplements come in a variety of forms, including: Pills, Tinctures, and Liquids. Feverfew: A Remedy for Migraine, in essence, feverfew is a blooming plant that often produces white blooms. The activity of feverfew is due to Parthenolides: This strong anti-inflammatory substance has the potential to lessen inflammation in the nerves. Sesquiterpene lactones: Generally speaking, they prevent the synthesis of molecules that cause migraines. In general, butterbur is an herbal medicine that works well for adult migraine prevention. There is proof that Petasites can prevent paediatric migraines, just like they do for adult migraines. Both Isopetasin and Petasin: Leukotriene production and inflammation are inhibited by these two chemical components. They can be discovered in the Petasites leaf and rhizome extract. Aromatic oils, alkaloids pyrrolizidine are also present within the plant. Ginger has been recommended as an efficacious home remedy for the treatment of migraine as an acute treatment, it relieves both headache and associated nausea. "Ginger juice", is an effective recipe in which half a tablespoon of ground ginger is stir into a glass of water and can be taken as herbal tea. Ginger has shown potential analgesic efficacy, 500 to 600 mg of ginger powder when taken with water for at least two to three times a day is reported to be efficacious against migraine. The analgesic activity of ginger is due to the chemical constituents present in it, these chemical constituents are gingerols and shogaols, they generally inhibit the prostaglandin biosynthesis by leading a decrease in the expression of the cyclooxygenase-2 enzyme (COX-2). Peppermint is basically a fragrant herb obtained from the leaves of peppermint plant. It is most commonly used as teas, essential oils, and remedies, which provides numerous health benefits. Peppermint has a cooling effect which generally inhibits the muscle contractions in the neck and the head region and also stimulate the blood flow to the area. This cooling sensation comes from the volatile component present in the plant extract i.e. menthol. Peppermint oil mainly has anti-inflammatory, analgesic, anti-infectious, antimicrobial, antifungal, vasoconstrictor, decongestant and stomachic properties. Turmeric is basically a flowering plant from the ginger family. It is usually a perennial herb native to the Indian subcontinent and southeast of Asia. It is obtained from the rhizomes of the plant '*Curcuma longa*'. The rhizomes are used fresh, boiled with water or dried; the further process involves grinding them into fine powder. Turmeric is a natural detoxifier, pain reliever and anti-inflammatory agent. The main mode of action is still unknown but hypothetically, it acts mainly by inhibiting the inflammation and reducing the pain.

Conclusion

Migraine is basically chronic headache disorder categorized by recurrent attacks lasting for 4- 72 hours, basically of moderate to severe intensity provoked by routine physical activity, generally associated with nausea, photophobia, vomiting. From this study we came to a conclusion that herbal drugs are effective treatment in the prophylaxis of migraine, with less or very few number of side effects the herbal remedies can be proven efficacious. Herbal remedies can help you to turn off the initial signs of a migraine attack, they can help to improve the quality of life mainly by reducing stress levels, help in getting good quality sleep. But one must be careful especially with herbal supplements, taking too much

or mixing with the other medications can be risky. One should always consult a doctor before taking a new supplement, this can reduce the risk and can increase the efficacy of the treatment. The myriads of resources were insighted to explore all the related data that is mentioned above, from the various digital platforms like PubMed and Google scholar. This analysis centres on the dominant significance of phytoconstituents in the management of migraine. Diverse studies reviewed above validate the usefulness of herbal remedies in migraine.

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