Chapter 1

Review of Antimigraine literature
1.1 Introduction

The history of man suffering from headache dates back to 5000 years BC when basic but drastic therapy practiced was trepanation. Ancient Egyptians documented in medical records headache with neuralgia as early as 1200 BC. Hippocrates, the father of medicine described the visual aura that normally precedes the migraine headache followed by vomiting which provided some relief. Proper description of migraine as unilateral paroxymal head pain accompanied by hypersensitivity to light (photophobia), hypersensitivity to sound (phonophobia) goes to Artaeus of Cappadocia. Recurrences of the above syndrome coupled with remissions of symptoms were termed by him during the second century as heterocrania.

Bibliotheca Anatomica Medic Chirurgica published from London in 1712 described four types of headaches, which included the “Megrim” identified as migraine. A paper published by Graham and Wolf in 1938 advocated the use of ergotamine tart as a good remedy for getting relief from migraine. An experimental approach was developed to study the mechanism of migraine in 1950 by Harold Wolff who put forth his vascular theory for migraine, which was criticized.

The term ‘Hemicrania’ was coined by Galenus of Pergamon from which the word migraine, which is of French origin, was derived. He assumed that migraine was due to the interaction of stomach and brain, as nausea and vomiting are observed during the migraine attack. The term Hemi-crania means the part affected by the attack is half portion of the head (hemi = half), which is the characteristic symptom of migraine.

1.2 Signs and Symptoms:

Periodic painful headache affecting the right or left part of the head is the characteristic feature of migraine. It is commonly preceded by
visual vaso-motor disturbances, nausea and vomiting. It may affect the neck, shoulders or arms. Palpitating sensation and throbbing are often experienced. The patients visualize oscillating zigzag lines separated by black areas. The patient is unable to bear the slightest sound such as people talking and cannot bear the diffused light also and prefers to lie down in darkness and soundproof room. The symptoms, which are common amongst patients, are divided into four types.

i. The **prodrome**, which occurs hours or days before the headache.
ii. The **aura**, which immediately precedes the headache.
iii. The **headache** phase.
iv. The **postdrome**.

**i. Prodrome phase**

This phase is characterized by the altered mood, irritability, depression or euphoria, fatigue, yawning, excessive sleepiness, craving for certain food (e.g., chocolate). These symptoms are observed in 40-60% of patients and they usually precede the headache phase of the migraine attack by some hours or even days. These symptoms actually serve as signals to impending attack of migraine.

**ii. Aura phase**

Symptoms of this type are usually sensory in nature and consist of focal neurological phenomena, which precede or accompany the migraine attack. The symptoms are experienced for a short period of around fifteen to twenty minutes and subside before the headache starts. During neurological events visual aura is the most common feature, which is marked by the disturbance of vision consisting of unformed flashes of white or rarely of multicolored lights (photopsia) or
formations of zigzag lines (teichopsia). Some patients also experience blurred, shimmering or cloudy vision.

The second sensory aura is the somatosensory aura, which is characterized by digitolinguial or cheiro-oral paresthesias. During this phase the patients experience a prickly feeling of pins and needles in the hand, arm and in the ipsilateral nose-mouth area. The above paresthesia gradually moves towards the arm, face, lips and tongue.

iii. Headache phase

A typical migraine headache is commonly unilateral with moderate to severe throbbing, which gets aggravated by physical activity. Bilateral pain is also sometimes experienced at the onset of the attack. Alternatively the unilateral headache may spread to both the sides of the head. It is also observed that the attack occurs on both the sides in an alternative fashion. The pain due the headache reaches the peak and then gradually diminishes during a period of 4-72 hrs in adults and 1-48 hrs in children. The frequency of migraine attack and the intensity of the pain due to headache are variable and are usually accompanied by anorexia and nausea. Some patients also experience occasional vomiting. Headache phase is marked by blurred vision, stuffy nose, diarrhea, polyurea, pallor and sweating in addition to these symptoms localized edema on the scalp and face, tenderness of the scalp, throbbing of a vein or artery in the temple and stiffness and or tenderness in the neck are experienced by the patient during this phase. Further lack of concentration, changing mood, and lightheaded feeling and body imbalance are also commonly found in patients.
iv. Postdrome phase

During this phase the patient feels exhausted, irritable, and listless and lacks concentration power. Tenderness in the scalp and alterations in the mood are also quite often experienced. The interesting part of this phase is that some patients feel refreshed or euphoric while some face depression and malaise.

1.3 Pathophysiology:

The exact cause of migraine headache is not still very clear. Migraine episode is fairly irregular and there is no explanation as to the attack of migraine at a particular time and not at any other time period. Further a migraine trigger factor, which on either exposure or withdrawal results in the onset of acute migraine headache. Generally the trigger factors are classified as behavioral, environmental, dietary, chemical, physiological or hormonal. The trigger theory is fairly well accepted and the trigger factors consist of stress, anxiety, excitement, fatigue, anger, over illumination of light or its glare, alcohol, particular food, excess or insufficient sleep and weather (hot sun or too cold conditions). In addition, migraine attacks could be due to irregular intake of food, fasting for a long period and over sensitivity to certain issues (psychological). Migraine attacks are noticed when there is an increased plasma level of steroidal hormones such as oestradiol and progesterone.

1.3.1 The headache is considered to be due to increased blood flow in both intracerebral and extracranial blood vessels, which cause increased pulsations of cranial arteries especially menengial branches of external carotid. Pain experienced during migraine is considered to be due to arterial pulsation. The visual disturbances are attributed to
the constriction of blood vessels in the visual areas of the brain. Similarly during or before the attack it seems that there will be decrease in the blood flow in some cerebral regions.

Relief from migraine pain cannot be felt by increasing the intracranial pressure indicating that the affected vessels are located outside the skull. They are probably branches of the external carotid artery. In support of this it has been observed that if the carotid artery on the affected side is occluded by pressure on the neck, the intensity of the headache is diminished.

1.3.2 Common causes of migraine include stress, anxiety, excitement, fatigue, anger and exhaustion. Under stressful conditions some hormones such as adrenaline, nor adrenaline, and arachidonic acids are released which cause common disorders of blood known as platelet aggregation. Other reasons of migraine attack are considered to be intake of certain food material, irregular intake of food, fasting for a longer period, long exposure to hot sun and weather, and over sensitivity to certain issues. In some cases increased plasma levels of steroidal hormones such as oestriadiol and progesterone are associated with migraine. Although the etiology of the disease is not well understood many hypotheses are put forward supported by very few in-vivo and clinical trials.

1.3.3 Historical background: Aggressive yellow bile was thought to be responsible for migraine attack by the followers of Gulenus. In his text book entitled 'El Qanoon fel teb' Ebn Sina attributed the migraine pain due to small movements, drinking, eating, food and sound. In the case of women, Abu Bakr Mohammad Ibn Zakariya postulated that post delivery conditions, post abortion period and menopause
 syndromes and dysmenorrhea were the real causes of migraine headache.
An overactive sympathetic nervous system was considered to be a predisposing factor for migraine during 1920. Later observations postulated the causes of migraine to the changes in the amplitude of pulsations of certain branches of the external carotid arteries. To prove this point the manual pressure exerted on the common carotid artery reduced the amplitude of pulsations, which in turn reduced severity of pain due to migraine. The pulsation theory led to divide the migraine syndrome in three phases. During the first phase constriction of the cerebral vessels is observed. The second phase consists of marked arterial pulsations, which involve throbbing and pain. The third phase results in arterial rigidity with continued pulsations, excruciating head-pain, nausea, vomiting and xerostomia. It was also observed that vasoconstriction by a specific drug such as ergotamine caused reduction in pulsations.

1.3.4 It was later observed that migraine was related to change in the amplitude of pulsations of certain branches of the external carotid arteries. It was shown that a reduction in the amplitude of pulsations of the temporal artery caused by manual pressure on the common carotid artery produced diminution in the severity of the migraine’s pain. Ergotamine tartrate was shown to diminish the amplitude of arterial pulsation to about 50% with the concomitant relief of pain.

1.3.5 Migraine syndrome has been further studied in some detail. The episode was divided into three phases. The first phase is related with marked constriction of the cerebral vessels. The second phase is accompanied by marked arterial pulsations (throbbing and pain). The third phase shows arterial rigidity with continued pulsations. The symptoms of this phase are excruciating
head-pain, nausea, vomiting and xerostomia. It was observed that the pulsations were diminished in the first phase due to the vasoconstricton on cerebral vessels by ergotamine and hence it was concluded that ergotamine could best be used as a prophylacting agent.

1.3.6 Modern approaches/Theories:

According to modern approach vasoactive monoamines, platelet aggregation, 5-hydroxytryptamine and prostaglandins play an important role in migraine. Monoamines such as adrenaline, nor adrenaline, 5-hydroxytryptophan, tyramine and β-phenylethylamine are partially broken down by the enzyme, monoamine oxidase (MAO). It has been observed that migraine is triggered when the level of monoamine in the blood exceeds the threshold limit, which varies from individual to individual. Platelet-MAO activity is reduced during the attack by migraine. However the platelet-MAO activity is increased with the advancement of age, resulting in the reduction in the severity and frequency of migraine attack. In the case of women suffering from migraine platelet-MAO activity is increased to reach the peak during ovulation, when female sex hormones are released. This triggers the migraine attack in some women before their menstrual cycle begins.

1.3.6.1 Role of platelet aggregation in migraine:
Platelet aggregation was clearly observed during migraine attack and this increase was considered to be the major factor in the pathogenesis of migraine. It was deduced that stress causes an increase in the plasma level of adrenaline, nor-adrenaline and arachidonic acid, which in turn causes platelet aggregation. The detection of increased plasma levels of PAF in patients with cirrhosis of
lever and the increased sensitivity of platelets of migraine sufferers\(^1\) to PAF are amongst the newest area of potential application of PAF antagonists. While it is likely that not all the pathophysiological states in which PAF is implicated as a mediator will be treatable with PAF antagonists the likelihood that some of these disease-states especially the less acute in nature might succumb to such an agent cannot be dismissed\(^2\).

1.3.6.2 Role of 5-hydroxytryptamine (5-HT)

5-Hydroxytryptamine also known as serotonin is responsible for the vasoconstriction. In the human body 90\% of 5-HT is localized in the intestine and the remaining in the platelet and the brain. The sudden rise in the level of plasma 5-HT after platelet aggregation results in the prodromal symptoms of migraine mentioned earlier. In fact, the plasma 5-HT level is elevated before the onset of headache phase. It has been observed that level of 5-Hydroxy indole acetic acid, a metabolite of 5-HT, increases during attack and hence it is excreted. A rapid rise followed by the reduction in 5-HT levels is also a cause of migraine attack. In addition to the changing levels of 5-HT plasma catecholamines are also responsible for the migraine attack\(^3\).

1.3.6.3 In the baboon, infusion of 5-HT into the external carotid artery increases its blood flow by several hundred percent. This is the opposite effect observed with respect to internal carotid artery. Some branches of the external carotid artery including middle meningeal pass through the skull. These are some sites of pain during migraine. Similarly the other sites of pain are the branches of middle meningeal artery extending over the temporal and parietal area of the skull and into the orbit.
1.3.6.4 It was observed that migraine occurred when there was a sudden and rapid destruction of platelet. Further, as per the study, a rapid rise followed by a fall in 5-HT levels is a prerequisite for migraine attack.

Although changes in the 5-HT levels appear to be the major factors in the vascular effects caused by the change in the levels of plasma catecholamines are also considered to contribute significantly to migraine attack.

1.3.6.5 Role of Prostaglandins in migraine:
The pain-producing substances called Prostaglandins (PGs) have been found to be responsible in the pathogenesis of migraine\textsuperscript{3,4,5} that it appears results from extracranial vasodilation, inflammation and hyperalgesia consequent to arterial distention. Amongst PGs the vasodilators belong to E series which sensitize the algogenic actions of other mediators such as bradykinin and 5-HT. Both these have been implicated in the migraine attack. In support of this it has been observed that both PGE-1 and PGE-2 induce migraine in volunteers who have not been exposed to migraine attack\textsuperscript{6,7,8}. As a result the symptoms of migraine such as flushing, nausea, severe headache and in some cases visual disturbances are observed.

1.3.6.6 Pulmonary release of prostaglandins triggered by the migraine attack due to 5-HT release from blood platelet is considered to be responsible for the pathophysiological changes\textsuperscript{9}. This is in agreement with the finding that 5-HT releases prostaglandins in the lungs of rats and guinea pigs\textsuperscript{10}. The fact the prostaglandin synthase inhibitor such as aspirin and paracetamol give relief to the pain due to migraine supports the view that prostaglandins are implicated\textsuperscript{11}. There is no evidence regarding the increased level of plasma prostaglandins by way of their measurement\textsuperscript{12}. Further, the fact that simple analgesics
such as aspirin and paracetamol give relief only partially suggests that PGs are not the primary or the only mediators responsible for migraine. It is possible that PGs are of secondary importance along with other factors. Similarly thromboxane synthase inhibitor did not give relief in migraine proving, that platelet-derived thromboxane A₂ enzyme is not responsible for migraine.¹³

1.3.6.7 In 2005, it was reported that in some people with a patent foramen ovale (PFO), a hole between the upper chambers of the heart, triggered migraine attack and that attack was prevented when hole was blocked. Several clinical trials are currently under way in an effort to determine if a causal link between PFO and migraine can be found. Early speculation as to this relationship has centered on the idea that the lungs detoxify blood as it passes through. The PFO allows blood to go directly from the right side of the heart to the left without passing through the lungs.

1.3.6.8 Etiology according to Ayurveda system:

As per the Ayurveda system of medicine, headache can be caused due to the disorders of VATA, PITTA and KAPHA. Ardhavabhedaka, is term used in Ayurveda for migraine. Vata headache is characterized by extreme pain, anxiety, depression, constipation and dry skin. It gets aggravated by lack of sleep, irregular diet, excessive activity, mental stimulation worry and stress. Majjivaha srotas especially the brain is affected in this kind of disorder. Symptoms of Pitta (Fire) headache are burning sensation, red face and eyes, sensitivity to light, anger, irritability and some times bleeding nose. It is often associated with liver disorders or impure blood conditions.
Kapha (water) type is more a dull headache with feelings of heaviness and tiredness. There may be nausea, phlegm, excessive salivation or
vomiting. It is usually caused by the congestion or phlegm in the head and may be associated with pulmonary disorders.

1.4 Migraine Triggers:

Many people report that one or more dietary, physical, hormonal, emotional or environmental factors precipitate their migraines. The most-often reported triggers include stress, over-illumination or glare, alcohol, foods, too little sleep and weather. Sometimes the migraine occurs with no apparent cause.

It is advisable for Migraine patients to try to identify personal headache triggers by finding out the links between their headaches and various suspected trigger factors. It is better to keep a “headache diary” which records what they eat and when they get a headache. These correlations can help to avoid headache by avoiding factors identified as triggers.

1.5 Treatment:

Conventional treatment focuses on three areas: trigger prevention, symptomatic control and preventive drugs.

Patients can attempt to identify and prevent factors that promote or precipitate migraine episodes. Moderation in alcohol and caffeine intake, consistency in sleep habits and regular meals may be helpful. Beyond an often-pronounced placebo effect, general dietary restriction has not been demonstrated to be an effective approach to treating migraine.

The drugs used in the treatment of migraine are divided in to two classes:

**Prophylaxis**: Preventive treatment for migraine headaches is called migraine prophylaxis or prophylactic therapy. Prophylactic medications
are administered to prevent the attack before the onset of migraine. They have three purposes:

- To lower the frequency and severity of the patient’s headaches.
- To make acute migraines more responsive to abortive treatment.
- To improve the overall quality of the life of migraine patients.

**Acute Treatment:** Treatment, which is administered to stop or ease the pain of a migraine headache after its onset is known as acute or abortive treatment.

1.5.1 **Prophylaxis** - β-Blockers are widely used as migraine prophylactic medications. 50-70% of patients get relief from these β-Blockers.

Beta-blockers that have been approved by FDA for migraine therapy are propranolol (Inderal) and timolol (Tenormin)

Propranolol: This is a β-Blocker that exhibits prophylactic action and is not effective if taken after the onset of an attack. There is some evidence that its effectiveness is enhanced with the increased period of dosing. For example patients who receive the drug for one year, experience greater benefit than those who have been administered the drug for 3 months\textsuperscript{14}. Propranolol’s activity as an antimigraine compound was a serendipitous discovery as it was primarily undergoing clinical trials for angina and hypertension. The efficacy of propranolol has been confirmed\textsuperscript{15}. Unlike many other β-Blockers in this case lack of partial agonism seems to be important\textsuperscript{16}. Thus propranolol, timolol, atenolol (β-no agonism) are all effective; while oxprenolol, alprenolol and pindolol (β\textsubscript{1}/β\textsubscript{2} partial agonist) are not effective\textsuperscript{17,18}. Clinical trials pertaining to migraine are fairly difficult to carry out and the smaller trials may not lead to proper conclusion.
A number of mechanisms have been proposed for the anti-migraine effects of β-Blockers but none has achieved wide acceptance\textsuperscript{19, 20, 21, 22, 23}.

Dosage of propranolol ranges between 80mg-160mg/day.

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\begin{align*}
\text{PROPRANOLOL} & \\
\text{ATENOLOL}
\end{align*}
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\textbf{1.5.1.1 5-HT Agonists\textsuperscript{24}:}

Pizotifen: It is a partial agonist – antagonist of 5-HT receptors. In addition it shows anti-histaminic and anti-cholinergic activities. 0.5-1 mg TDS is effective but less pronounced than that of propranolol. Drowsiness, increased appetite and weight gain are the side effects.

\textbf{1.5.1.2 5-HT Antagonists\textsuperscript{24}:}

Methysergide: This has been marketed by Sandoz (Switz) under the trade name Sansert. This is a 5-HT antagonist and is less efficacious than propranolol. Prolonged treatment leads to visceral fibrosis, which
is a serious side effect. When propranolol and Pizotifen therapy fails this drug may be used.

1.5.1.3 Tropaserin\textsuperscript{24}:

This is a 5-HT antagonist and is marketed by Marrel Dow.

![Methysergide](image1)

![Pizotifen](image2)

![Tropaserine](image3)

1.5.1.4 Calcium channel blockers: These are most useful drugs in the treatment of patients who cannot take beta-blockers or have been diagnosed with coexisting hypertension. Some calcium channel blockers are in use for the treatment of a related syndrome known as cluster headache. For example flunarizine and nimodipine are quite effective and of these the former reduces the frequency of either classical or common migraine to the extent of 90%. It has also been
reported to be useful in childhood hemiplegic migraine. The maximum treatment required is only one to two months.

1.5.1.5 Tricyclic anti-depressants:
Tricyclic anti-depressants such as amitriptyline are less effective when compared with propranolol. However these can be tried on patients not responding to the latter.

![Chemical structures of FLUNARIZINE, NIMODIPINE, and AMITRIPTYLINE](image)

1.5.2 Drugs used in acute attack

Analgesics such as aspirin and paracetamol give fairly good relief in most of the mild attacks of migraine. Ergotamine\textsuperscript{24, 25} is one of the most effective drugs in the early attack and at lower doses the relief is dramatic. However, severe attacks require larger doses. Oral administration is preferred at doses of 1 mg at half an hour intervals till relief is obtained or a maximum of 6mg is administered. The drug is administered to patients suffering from severe nausea suppository through rectum. Parenteral administration is hazardous and is not recommended. A nasal preparation is also introduced in some countries. Since Ergotamine has no prophylactic action its regular use is not justified. Dull background headache is the main side effect and attack may recur on withdrawal of drug. Dihydroergotamine: Due to its low toxicity it can be used parenterally.
1.5.3 OTHER ANALGESICS USED IN MIGRAINE ARE SHOWN BELOW\textsuperscript{25}.

Volofane

Hommel, Switz.

Oxetorone

France

Metergotamine

Fermitalia, Italy
Trade name:
Liserdol
1.5.4 OTHER COMPOUNDS USED AS ANTIMIGRAINE AGENTS$^{25}$.

Sergolexole

Lilly

Alpiopride

Delarange, France
Trade name: Revestel

Flumedroxone-17-acetate

Loevans, Sweden
Trade name: Demigrana
1.5.5 Non-steroidal anti-inflammatory drugs\textsuperscript{26} (NSAID):

Anti-inflammatory drugs such as mephenamic acid and flufenamic acid, which are in action, have been found to be quite effective in the treatment associated with attack occurring during menstrual period. They are also reputed to be as effective as ergotamine in the treatment of common migraine.

\begin{center}
\begin{tabular}{c|c}
\textbf{MEPHANAMIC ACID} & \textbf{FLUFENAMIC ACID} \\
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1.6 Drug-Drug synergistic action in migraine\textsuperscript{27}.

1.6.1 Caffeine: Caffeine (100mg), administered in combination with ergotamine enhances its absorption from the oral and rectal routes and gives additive effect to the cranial vasoconstricting action. Many combination preparations are available.

1.6.2 An anti-emetic drug metacalopramide has been shown to increase the rate of absorption of aspirin\textsuperscript{28,29,30} illustrating the synergistic action of drugs.
Migraine is usually accompanied by gastric stasis, which in turn results in the poor absorption of oral analgesic, aspirin. This poor absorption by oral route is responsible for inadequate relief. In support of this hypotheses an experiment was carried out in which metaclopramide was introduced in to the gluteus maximum during a migraine attack and it was observed that aspirin absorption was significantly more. This was indicated by the plasma salicylate levels, which were double as compared to control patients where only aspirin was administered. It was further shown that patients with this combination therapy got faster relief than the treatment with aspirin alone. It was also concluded that the combination of metaclopramide and aspirin increased the absorption of aspirin at a faster rate prior to onset of migraine.

1.7 Triptans:

Sumatriptan and related selective serotonin receptor agonists are now the therapy of choice for severe migraine attacks that cannot be controlled by other means. They are highly effective in reducing the symptoms or aborting the attack within 30 to 90 minutes in 70-80% of patients. Some patients have a recurrent migraine later in the day and only one such recurrence in a day can be treated with a second dose of a triptan. They show few side effects if used in correct dosage and frequency. There have been some rare instances of cardiac arrest in patients using triptans. Some members of this family of drugs are:
1.7.1 Sumatriptan:
This is a triptan drug originally manufactured and marketed by Glaxo, UK for the treatment of migraine headaches. Several dosage forms for Sumatriptan have been approved including tablets, solution for injection and nasal inhalers. Sumatriptan was the first triptan available (in 1991), in the United States and other most developed countries. It is available only by medical prescription.
Mode of action: Sumatriptan is a 5-HT (5-HT_{1D}) agonist. The specific receptor subtype is present in the cranial and basilar arteries. Activation of these receptors causes vasoconstriction of the dilated arteries. Sumatriptan is also known to decrease activity of the trigeminal nerve.

1.7.2 Zolmitriptan:
This is an oral selective 5-hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist. It is a second-generation triptan for acute treatment of migraine attacks with or without aura and cluster headaches. Zolmitriptan is marketed by AstraZeneca with the brand names Zomig, Zomagon (Greece and Argentina) and AscoTop (Germany). Zolmitriptan is indicated for the acute treatment of migraine with or without aura in adults. Zolmitriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Zolmitriptan should not be given to patients with ischemic heart disease. It may cause hypertension and should not be administered to patients with uncontrolled hypertension.

1.7.3 Naratriptan:
It is developed by Glaxo Wellcome Inc. It is used for the treatment of migraine headaches and is a selective 5-hydroxytryptamine 1-receptor subtype agonist.
Vision changes, tingling sensations, tiredness or weakness, stomach upset, dizziness and warm/cold temperature sensations are some of the side effects.

1.7.4 Rizatriptan:
This is a second-generation triptan and is developed by Merck & Co. for the treatment of acute migraine headaches. It is a second-generation triptan for acute treatment of migraine attacks. It is available only by prescription in the US and Canada. This drug does not prevent future migraine attacks.

1.7.5 Eletriptan:
This is developed by Pfizer for the treatment of migraine headaches. It is available only by prescription in the US and Canada.

1.7.6 Frovatriptan:
It is developed by Endo Pharmaceuticals for the treatment of migraine headaches. Frovatriptan causes vasoconstriction of arteries and veins that supply blood to the head. Frovatriptan has mean terminal elimination half-life of approximately 26 hours, which is substantially longer than other triptans.

1.7.7 Almotriptan:
It is developed by Ortho-McNeil for the treatment of migraine headaches.
1.8 Side effects:

1.8.1 Abortive medications

In addition to the risk of rebound headaches, possible side effects of abortive medications include:

- Triptans: May cause tingling, numbness, sensations of heat or flushing, dizziness, drowsiness or pain at the injection site.
• Ergot alkaloids: May cause nausea, vomiting, diarrhea, weakness, itching, cold skin, thirst, tingling sensations and severe muscle cramps; also may cause severe rebound headaches. The most serious potential side effect of ergot alkaloids however is gangrene which is the death of tissue in the fingers or toes due to constriction of the smaller blood vessels and loss of blood supply to the tissue.

• NSAIDs: May cause heartburn, nausea and vomiting; may also cause drowsiness, dry mouth or mild depression.

• Combination analgesics: Midrin has been reported to cause temporary dizziness and skin rashes. The most common side effects of Fioricet and Fiorinal include lightheadedness, nausea and sleep disturbances. Also, the narcotics and barbiturates (Fiorinal) have the potential for drug abuse and dependence.

• Antiemetics: May cause anxiety, dizziness, low blood pressure, sedation, nausea, dry mouth and restlessness.

1.8.2 Prophylactic medications

The following side effects have been reported for prophylactic medications.

• Anticonvulsants: Valproic acid may cause indigestion and vomiting, hair loss, weight gain, changes in temper, hallucination and liver damage. Gabapentin and topiramate are associated with drowsiness, dizziness, tingling sensations, diarrhea, altered taste and fatigue.

• Beta-blockers: May cause dizziness, fatigue, nausea, memory problems, sexual dysfunction, bradycardia (slowed heartbeat) and hallucinations.
• Calcium channel blockers: May cause low blood pressure and constipation; in addition the headaches intensify for the first few weeks of treatment.

• TCAs: May cause dry mouth, constipation, difficulty in urinating, increased appetite, loss of sexual desire, heavy sweating, agitation, tremor and seizures.

• SSRIs: May cause loss of appetite or sexual desire, anxiety, drowsiness, nausea or flu like symptoms.

• NSAIDs: More likely to cause digestive problems when used for prophylaxis than when used for acute treatment.

• Serotonin antagonists: Methysergide has been reported to cause insomnia, abdominal pain, diarrhea, nausea, heartburn, increased sensitivity to cold and depression. Cyproheptadine may cause dry mouth, increased appetite and weight gain.

1.9 Botanicals in the treatment of migraine:
In view of the fact that most of the synthetic drugs used for treating migraine have side effects work on the development of plant-based drugs has gained momentum during the past two decades. Ayurveda system of medicine essentially consists of plant-based crude drugs. There are many such plants containing different active principles, which are being used to treat migraine both under mild and severe conditions. A continuing research is underway for obtaining better leads by screening plant extracts exhibiting anti-migraine activity. Some of the major plants used are:

1.9.1 Feverfew
1.9.1.1 Botanical Description of Feverfew
Botanical name :  Tanacetum parthenium (L) Schultz Bip
Family :  Asteraceae
Synonyms :  English : Fibrifuge, Mediaval aspirin
Latin : Febrifugia, Feverfew
Europe : Mother herb
German : Mutter krout
Other names: Summer daisy, Midsummer daisy, Nose bleed, Flirtwort, Bachelor’s buttons,
Chrysanthemum parthenium,
Pyrethrum parthenium.

1.9.1.2 Distribution and Habitat: It is a perennial and a strongly aromatic herb with a more or less vertical stock, an erect ridged somewhat downy stem 20-60 cm tall with strong smelling greenish yellow bipinnate leaves. The flower head are arranged in a loose terminal corymb, the central disc florets being yellow and a single layer of outer ray florets being white.

It grows in mountain terrains and waste places on the Balkan Peninsula. It was introduced in Britain and has since been cultivated as an ornamental and medicinal plant. It is now naturalized throughout Britain, Ireland and greater parts of Europe.

Leaves: Leaves are yellowish green, alternate, stalked, ovate and pinnately divided with an entire or crenate margin. The upper leaves have shorter stalks and are less divided.

Flowers: The flower heads are 12-22 mm in diameter long stalked in more or less lax, dense, corymbs of 5-30 such heads. The hemispherical involucres are 6-8 mm in diameter and the involucral bracts bluntly keeled and downy with narrow pale scraious margins and laciniate tips. Florates are white, short and broad with ligules 2-7 mm.
1.9.1.3 Feverfew\textsuperscript{31}: The most effective botanical source known today for the treatment of migraine is feverfew, \textit{Tanacetum parthenium} belonging to Asteraceae family. The widespread use of feverfew started in 1978 when the British press reported the beneficiary effects of its leaves on migraine patients. Traditionally leaves of feverfew or its infusion have been used as a febrifuge, to regulate menstruation, labour pain, stomachache, toothache and insect bite.

1.9.1.4 Anti-migraine activity of feverfew:

i) Collier et al\textsuperscript{32} in 1980 showed that the feverfew extract inhibited the prostaglandin synthesis in bull seminal vesicles, which was further confirmed by Pugh and Sambo\textsuperscript{33}. Further work by Thakkar et al\textsuperscript{34} revealed that feverfew extract inhibited the enzyme phospholipase A\textsubscript{2} of aortic smooth muscle and inhibited the formation of both cycloxygenase and lipoxygenase products in the peritoneal leucocytes of rats.

ii) Feverfew extract was shown to inhibit platelet aggregation induced by adenosine diphosphate (ADP), colleagen or thrombin by Makheja and Bailey\textsuperscript{35} for the first time who confirmed the inhibition of prostaglandin synthesis in platelets which indicated the involvement of the enzyme phospholipase A\textsubscript{2}. However, Heptinstall et al\textsuperscript{36} contradicted the results of Makheja and Bailey during their experiments which revealed that platelet aggregation induced by adrenaline, collagen and U46619 was inhibited by feverfew extract which reversed the platelet aggregation induced by ADP.

iii) Feverfew extract inhibited thromboxane–B\textsubscript{2} synthesis when platelets were stimulated by adrenaline. However when platelets were stimulated by ADP, arachidonic acid or thrombin no inhibition of thromboxane was observed\textsuperscript{36}.
iv) Platelet 5-HT secretion induced by ADP, adrenaline arachidonic acid was inhibited by feverfew extract in a dose-dependent manner. Similarly secretion induced by collagen and U46619 (a stable thromboxane A₂ mimic), phorbolesters and agents that activate protein kinase C was inhibited. However, Feverfew extract did not inhibit platelet aggregation or platelet 5-HT secretion induced by calcium ionophore A23187 at a higher dose while at a lower dose inhibition was observed³⁷,³⁸.

v) Feverfew extract was found to inhibit secretary responses, measured as vitamin B-12 binding protein release, induced by chemotactic peptide (FMLP) and calcium ionophore A23187 in a dose-dependent fashion in neutrophils³⁷. (Polymorphonuclear leucocytes). Similar inhibition was observed when induced by arachidonic acid.

vi) Feverfew extract was shown to inhibit neutrophil killing activity³⁹.

vii) It was found that feverfew extract inhibited mitogen-induced human mononuclear cell proliferation⁴⁰.

viii) Feverfew extract was shown to exhibit inhibition of histamine release induced by IgE A23187 in most cells⁴¹. It was also shown to reduce the spasmyolytic activity of smooth muscle induced by acetylcholine, 5-HT, histamine, prostaglandin E₂ and bradykinin.

1.9.1.5 Mechanism of action: The exomethylene group of the α-methylene butyrolactone moiety present in the biologically active sesquiterpene lactones in the feverfew extract reacts irreversibly with acid soluble sulphydryl (SH) groups by Michael-type addition reaction⁴¹,⁴²,⁴³,⁴⁴. These SH groups in platelets belong to glutathione (GSH)⁴⁵,⁴⁶ which is a cofactor for enzymes such as peroxidase. Since
these enzymes are inactivated by feverfew extract containing sesquiterpene lactones, arachidonic metabolism leading to prostaglandins and thromboxanes is impaired. Further feverfew extract inhibited the release of arachidonic acid from phospholipids indicating the inactivations of phospholipase A₂.

In support of the SH groups interacting with the α-methylene group of parthenolide and sesquiterpene lactones a reduction in the number of acid soluble SH groups in neutrophill in concentrations required for neutrophill inhibition was observed³⁸.

1.9.1.6 Results of feverfew in in-vivo models: Bronchoconstriction inhibition⁴⁷ induced by collagen was inhibited in guinea-pig models confirming the inhibition of phospholipase A₂.

1.9.1.7 Results in ex-vivo experiments
i) Inhibition of platelet aggregation induced by ADP or thrombin was not observed even after prolonged use of feverfew in 10 patients⁴⁷.

ii) Reduction in 5-HT secretion in platelets was not observed in 59 patients after administering feverfew for a period of four months⁴⁸.

1.9.1.8 Results of clinical trials:
i) During a clinical trial involving 17 patients it was clearly observed that feverfew had a prophylactic effect in getting relief from migraine⁴⁹.

ii) A double blind, randomized trial of 59 patients revealed the beneficial effects by the prevention of migraine⁵⁰.
iii) A study consisting of 40 patients suffering from rheumatoid arthritis showed that feverfew had no effect for the duration of the trial for 6 weeks\textsuperscript{51}.

iv) Feverfew caused contact dermatitis in hypersensitive patients as many sesquiterpene lactones are reported to be responsible to cause allergic contact dermatitis\textsuperscript{52,53}.

1.9.1.9 Commercial preparations:
Many commercial preparations are available in UK and USA.
i) The preparations consist of the powdered dried leaf in tablet or capsule form.
ii) The preparations consist of the powdered whole plant in tablet or capsule form.
iii) The content of the preparations vary from 25 mg to 390 mg per tablet or capsule. However, it was observed that this dosage was found to be inadequate for the platelet antisecretory activity indicating the need for standardization of the drug\textsuperscript{54}.
iv) The quantity of parthenolide in the capsule containing the dried leaves with an average weight of 82 mg was found to be 0.67% on its activity basis\textsuperscript{50,51}.
v) Commercial products of USA were found to contain less than 0.1% parthenolide.
vi) Health Protection Branch of Health and Welfare, Canada\textsuperscript{55} recommend a minimum of 0.2% parthenolide in commercial product.
vii) Estimation of parthenolide by different analytical methods has been reported\textsuperscript{56}.

1.9.1.10 Chemical constituents: Czech workers\textsuperscript{57} were the first to initiate the chemical investigations on feverfew and they named a sesquiterpene lactone isolated as parthenolide. However, its structure
was later on revised by Govindachari et al.\textsuperscript{68}. It is a germacranoilide type of sesquiterpene lactone. Its structure was confirmed later by X-ray crystallography\textsuperscript{59}. Later on Romo-de Vivar et al.\textsuperscript{60} examined the constituents of \textit{T. parthenium} grown in Mexico but surprisingly were not able to detect parthenolide.; instead isolated and characterized a closely related compound named as santamarine. This is one of the illustrations where occurrence and concentrations of constituents from different sources vary due to geographical factors. Further work by various workers resulted in the isolation of more sesquiterpene lactones namely canin\textsuperscript{61,62} and artemcanin\textsuperscript{61,62}, reynosin\textsuperscript{63}, 8\(\beta\)-hydroxyreynosin\textsuperscript{63}, 1\(\beta\)-hydroxyarbusculin\textsuperscript{63}, magnolialide\textsuperscript{62}, constunolide\textsuperscript{63}, 3\(\beta\)-hydroxycostunolide\textsuperscript{64}, artemorin\textsuperscript{64}, hydroxy ketone, epoxide and ketone corresponding to artemorin and 8\(\beta\)-hydroxyestafiatin\textsuperscript{64}. Further series of compounds include diepoxide\textsuperscript{64}, two endoperoxides\textsuperscript{64}, tanaparthin \(\alpha\)\textsuperscript{64} and tanaparthin \(\beta\)-peroxides\textsuperscript{64}, two secoguianolides\textsuperscript{64}, secotanaparthalide A & B\textsuperscript{64}, partholide\textsuperscript{64}, chrystamemolide\textsuperscript{64}.

![Chemical structures](image-url)

**PARTHENOLIDE**

**3\(\beta\)-HYDROXY PARTHENOLIDE**

**SANTAMARINE**
1.9.1.11 Anti-Migraine activity of individual active principles

i) Inhibition of prostaglandin synthesis was confirmed and the three active compounds identified were parthenolide, chrysanthenyl acetate and michefuscalide\textsuperscript{33}. It is postulated that in the case of chrysanthenyl acetate inhibition could be due to acetylation of cyclooxygenase part of prostaglandin synthetase complex similar to aspirin\textsuperscript{34}.

ii) Similarly, the compounds responsible for inhibiting 5-HT secretion in platelets were identified as\textsuperscript{65} parthenolide, canin, artecanin, secotanapartholide and 3β-hydroxytanapartholide.

iii) Parthenolide inhibited platelet 5-HT secretion in the micromolar concentration\textsuperscript{37}.

iv) Parthenolide was found to inhibit mitogen induced human mononuclear cell proliferation, which is the same as cytotoxic effect\textsuperscript{40}.

v) Parthenolide was shown to protect induced nephrocalcinosis\textsuperscript{66} in rats indicating the inhibition of prostaglandin synthesis as prostaglandins are supposed to be responsible for nephrocalcinosis.

Side Effects:
Pregnant women should not use feverfew as it may stimulate uterine contractions. It may also cause mild indigestion in some people. Patients who use fresh plant leaves rather than standardized preparations may experience mouth ulcers or temporary loss of taste. Also patients who use fresh plant leaves cannot regulate their doses; if it is not standardized.
1.9.2 Alternative of feverfew

Feverfew is a plant growing at high altitudes and or in the temperate and sub-temperate zones of Britain, USA and Europe. Tropical climate of India except Himalayan terrain is not suitable for its cultivation and hence its supply has to be through imports from European countries, which may not be sometime economical. During the literature survey of various plant species containing parthenolide, responsible for the anti-migraine activity, *Michelia champaka* belonging to Magnoliaceae appeared to be a good candidate and some preliminary work was carried out at the Indian Drug Research Association, Pune and the National Chemical Laboratory, Pune, regarding the commercial viability of this plant by estimating the content of parthenolide\(^67\).

1.9.2.1 *Michelia champaka* Family, Magnoliaceae

Vernacular synonyms:

- Sanskrit : Champaka, Kasuma, Suvarna, Hemapushpa
- Bengali & Hindi : Champa, Champaka
- Gujarati : Rae Champec, Pilu champa
- Kannada : Sampige
- Marathi : Sonchapha, Kudchapha
- Telagu : Champakamu, Sampangi, Champakmi
- Tamil : Sembagam, Shampangi, Chembuga, Shampang.

1.9.2.2 Properties described in Ayurvedic literature:

- Tikta, Katu, Kashaaya
- Veerya: Sheeta
- Guna: Laghu, Rooksha
- Vipaka: Katu

1.9.2.3 Vishahara, Krinihara, dahanashana, Kadoohara, mootrakricchrahara\(^68\).

Vaatraktahara, Kaphapittaghna, Vranhara, Kushtahara and
1.9.2.4 Distribution and habitat

Indigenous and distributed throughout India including Eastern Himalayas. It is commonly cultivated for ornamental purposes, for its sweet scented golden colored flowers. It is a large evergreen tree reaching up to 30m in height and 3.5 m in girth.

1.9.2.5 Biological activity:

The bark is considered as a febrifuge, stimulant and expectorant and used in chronic rheumatism. Infusion of the root and root bark is used as a purgative and emmenagogue with curds. The fruits and flowers are known to be stimulant, antispasmodic, tonic, stomachic, carminative bitter and cooling. It is also reported to be diuretic in renal disease and gonorrhea. The oil of the flowers finds its use in cephalalzia, ophthalmia, gout and rheumatism.

1.9.2.6 Chemical constituents:

Chatterjee and Majumdar\(^6^9\) isolated an alkaloid liriodenine from the stembark of *M. champaka*. It was found to be identical with thalictrane. A new sesquiterpene hydrocarbon, champacene was reported by Nigam\(^7^0\). An alkaloid macheline A was reported by Banerjee and Chakravarti\(^7^1\).

Govindachari and co-workers\(^5^8\) while working on the root bark isolated parthenolide and liriodenine. They corrected the structure earlier proposed by Czech workers to parthenolide.

The essential oil\(^7^2\) from the fruit rind was analyzed as consisting of 1,8 cineole, phenethylalcohol, pinocamphene, linalool, ester of pinacamphol, pinocamphol, phenethylacetate and \(\alpha\)-phellandrene
while the essential oil from the leaves comprised of linalool, linalyl acetate, methylheptanone and geraniol\textsuperscript{73}.

From the hexane extract of the root bark four sesquiterpene lactones were reported by Sethi et al\textsuperscript{74} and they were identified as costunolide, parthenolide, dihydroparthenolide and micheliolide.

Bhimshankar Rao et al\textsuperscript{75} reported the isolation of a polyisoprenoid, \(\beta\)-sitosterol, \(\beta\)-sitosterol-3-O-\(\beta\)-D-glucoside and liriodenine from the extracts of leaves with different solvents.

As per the report of Chatterjee and Pakrashi\textsuperscript{76} the plant contains in addition a compound identified as magniflorine.
1.9.2.7 Estimation of parthenolide in various parts of _M. champaka_.
Recently Baluragi _et al._ have carried out a comparative study of the occurrence of parthenolide in different parts of _M. champaka_ and the leaves of _Tanacetum parthenium_ quantitatively by HPLC methods and the results are shown in Table 1.

**Table 1**: Parthenolide content on dry RM basis

<table>
<thead>
<tr>
<th></th>
<th><em>M. champaka</em></th>
<th><em>Tanacetum parthenium</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td>0.064%</td>
<td>0.248%</td>
</tr>
<tr>
<td>Stem</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Roots</td>
<td>0.1729%</td>
<td></td>
</tr>
</tbody>
</table>
From these results it appears leaves of *M. champaka*, which are a regenerative resource, can be supplemented with the cultivated feverfew in India for the formulation of the drug containing the active principle, parthenolide.

1.9.3 *Petasites hybridus* (Butterbur)

50 mg to 75 mg/day of Butterbur (*Petasites hybridus*) rhizome extract was shown in a controlled trial to provide 50% or more reduction in the number of migraines to 68% of participants in the 75mg dose group, 56% in the 50mg dose group and 49% in the placebo group after four months. Native Butterbur contains some carcinogenic compounds, but a purified version, Petodolax®, does not. The side effects reported for preparations made from butterbur root are rare, but include an unpleasant taste in the mouth, belching, and a mild skin rash in some patients.

1.9.4 Cannabis:

It was a standard treatment for migraines from the mid –19th century until it was outlawed in the early 20th century in the USA. It has been reported to help people through an attack by relieving the nausea and dulling the head pain. There is some indication that semi-regular use may reduce the frequency of attacks. Further studies are being conducted.

1.9.5 *Pueraria lobata* (Kudzu root):

It has been demonstrated to help with menstrual migraine. It is assumed that Kudzu acted by imitating estrogen, it has since been shown that Kudzu has significant effects on the serotonin receptors.
1.9.6 Other plants: Decongestant and expectorant herbs such as Calamus, Ginger, Bayberry, Angelica, wild Ginger and sacred Tulsi are commonly used during the mild attacks of migraine. Calamus powder is snuffed or its ghee applied to the inner nose. Similarly tulsi in the form of tea works effectively. Ginger paste, which is known for its anti-prostaglandin activity is applied to the lower nose and temples. Some of the essential oils used for external application during mild migraine are camphor, Wintergreen, Eucalyptus and Sandalwood oil.

Purgation is quite useful in migraine as the colon is the main site of the problem. Triphala churna as a mild purgative appears to give good relief. Other useful herbs include Valerian, Jatamansi, Chamomile, *Acorus calamus*, Gotukola, Aloe, Rhubarb and a formula known as Saraswat powder. Since migraine requires adequate sleep herbal sedatives are recommended. Similarly functioning of lever should be normal as it prevents the migraine attacks. As a lever tonic Gotukola alone or in combination with Passion flower is recommended. In chronic cases long-term tonic therapy with Chavanprash or Ashwagandha are prescribed. Herbs of choice are flowers of Arka (*Calotropis procera*), *Camphora officinarum*, Eranda (*Ricinus communis*), Shatavari (*Asparagus racemosus*), Tulsi (*Ocimum sanctum*), Bhringaraj (*Eclipta alba*), Saptaaparni (*Alstonia sholaris*) Vavidang (*Embelia ribes*).

1.10 Contra-indications

Patients who are taking any antimigraine drug should make sure to give the doctor a list of all other medications that they take on a regular basis, including over-the-counter pain relievers, herbal preparations, and any special herbal or medicinal teas or extracts.

1.10.1 Abortive medications

The following interactions have been reported for abortive medications:
• Triptans: All the triptans narrow coronary arteries by 10-20% and will intensify the effects of other vasoconstrictive drugs, including the ergot alkaloids and drugs given for vascular disorders. With the exception of naratriptan, the triptans cannot be taken together with MAO inhibitor antidepressants because of the risk of a rapid and dangerous rise in blood pressure. Rizatriptan has been reported to interact with the beta-blocker propranolol.

• Ergot alkaloids: Cannot be taken together with methysergide because of an additive effect. Should not be taken together with other vasoconstrictive drugs (including beta-blockers, some acid-reducing drugs, some antibiotics and some antifungal drugs because of the increased risk of gangrene.

• NSAIDs: These drugs tend to prolong bleeding time and should be used cautiously by patients taking blood-thinning medications. Alcoholic beverages increase the risk of gastric ulcers or bleeding from the use of NSAIDs. In addition, patients should not take more than one NSAID at a time.

• Combination analgesics: These drugs should not be used together with MAO inhibitors or other drugs that contain acetaminophen. They will intensify the actions of other drugs that may cause drowsiness, including alcohol, TCAs, antihistamines, sedatives and muscle relaxants.

• Antiemetics: Should not be taken together with alcohol (intensifies central nervous system depression), tricyclic antidepressants (lowers blood pressure), or Phenobarbital. Patients taking anticonvulsants may need to have their dosage increased if they are given an antiemetic.

1.10.2 Prophylactic medications
The following interactions have been reported for prophylactic medications:
• Anticonvulsants: Valproic acid will intensify the effects of other anticonvulsants, barbiturates, alcohol and antidepressants. It interacts with aspirin and heparin to increase the risk of spontaneous bleeding. Gabapentin intensify the effects of morphine, but is less effective when taken together with antacids.

• Beta-blockers: Antacids decrease the absorption of beta-blockers. Cimetidine is reported to intensify the actions of beta-blockers. Beta-blockers may interact with insulin or other diabetes medications to produce high blood sugar levels. They should not be taken together with MAO inhibitors because of the risks of severe high blood pressure. Cocaine also increases the risks of high blood pressure or other heart problems in patients taking beta-blockers.

• Calcium channel blockers: Verapamil may cause low blood pressure or dizziness if taken together with alcohol. It should not be taken with beta-blockers because of a risk of congestive heart failure or slowed heartbeat. Verapamil also intensifies the effects of cyclosporine and lithium.

• TCAs: Should not be taken together with barbiturates, alcohol, sleeping medicines or sedatives because they intensify central nervous system depression. They may also intensify the effects of certain antibiotics and antifungal medications. They may interact with bupropion to produce seizures. TCAs should never be taken with MAO inhibitor or SSRIs because of the risk of serotonin syndrome, a potentially fatal condition marked by fever, rapid changes in blood pressure, sweating, hyper reactive reflexes, delirium, nausea, vomiting and coma. Serotonin syndrome takes name from overly high levels of serotonin in the patient's nervous system that is produced by these drug combinations.

• SSRIs: Should never be taken together with other antidepressant medications because of the risk of serotonin syndrome. SSRIs
should not be taken together with herbal preparations particularly containing valerian or St. John's wort.

CAM preparations: Feverfew should not be used with anticoagulants as it intensifies their effects. It may also interfere with the body's absorption of iron. NSAIDs reduce the effectiveness of feverfew. No interactions with prescription drugs have been reported for butterbur root preparations.

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