

## **The herbal approach for the treatment of migraine**

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### **Summary**

Migraine is a periodic disorder consisting of paroxysmal unilateral headache, accompanied by nausea, vomiting, photophobia and/or phonophobia. A working definition of migraine is benign recurring headache and/or neurological dysfunction usually attended by pain-free interludes and often provoked by stereotyped stimuli. Migraine is more common in females, with a hereditary predisposition towards attacks and the cranial circulatory phenomenon appears to be secondary to a primary central nervous system disorder. Phytomedicine has offered alternative source of therapy for migraine sufferers, and provided some additional information about the pathogenesis of migraine. Feverfew (*Tanacetum parthenium*) and Butter bur (*Petasites hybridus*) are some of the plants that have been used for on based on the preclinical and clinical studies. The more intensive research on the plants based medicines in the treatment of migraine (hemicrania) would provide new hope for the development of novel ethno-leads towards the pharmacotherapy of migraine.

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### **Introduction**

The new millennium has ushered in an era of science that will revolutionize a great majority of our day-to-day activities and life style. Driven by chemistry, but increasingly guided by pharmacology and clinical sciences, drug research has contributed to the progress of medicine during recent times. An unprecedented advance in biological knowledge and vast improvement in methodologies are generating a cornucopia of drug targets creating big opportunities for the design of small molecules with great therapeutic potential.

The advent of molecular biology and genetic science is having a deep impact on drug discovery. Molecular pharmacology has revolutionized the process of drug discovery by enabling the precise control of the expression of drug targets such as receptors and enzymes.

Nature has been a source of medicinal agents for long time and an impressive number of modern drugs have emerged from natural sources, many based on their use in traditional medicine.

Determination of structure and nature of proteins associated with disease process is of vital importance for drug development. With the development of new molecular targets based on these proteins there is an increasing demand for novel diversified molecules for pharmacological evaluations. Natural products will play a crucial role in meeting such demands through sustained investigations.

Medicinal plants play a key role in the human health care. Majority of the world population relies on the use of traditional medicine, which is predominantly based on

plant material. The traditional medicine refers to a broad range of ancient natural healthcare practices like Ayurveda, Siddha and Unani. These medical practices originated from times immemorial and developed gradually, to a large extent, by relying or being based on practical experiences without significant references to modern scientific principles<sup>1,2</sup>.

Use of plants as a source of medicine has been inherited and is an important component of the healthcare system in India. In the Indian system of medicine, most practitioners formulate and dispense their own recipes; hence this practice requires proper documentation and research. Likewise, the use of herbal medicines is steadily growing in the western world, with approximately 40 per cent of the population reporting the use of herbs to treat medical illnesses within the past year. Public, academic and government interest in traditional medicines is growing exponentially due to the increased incidence of the adverse drug reactions and economic burden of the modern system of medicine<sup>3,4</sup>. The major hindrance in the amalgamation of herbal medicines into modern medicinal practices is the lack of scientific and clinical data, and better understanding of efficacy and safety of the herbal products. The traditional use can provide valuable clues for the selection, preparation and indications for use of herbal formulation, as efficacy has been established by the common use. The historical background provides the source of information to study the specific plant species to be used for a particular disease with great potential. Hence, a systematic approach, through experimental and clinical validation of efficacy, is required for a traditional medicinal plant, similar to the validation process utilized in modern medicine<sup>4</sup>.

Although herbal medicines are effective in the treatment of various ailments, very often these drugs are unscientifically exploited and/or improperly used. However, a detailed pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable herbal drugs for many dreaded diseases.

Ethnopharmacology has come to stay as interdisciplinary scientific exploration of biologically active agents, with traditionally observed beneficial effects in man<sup>2</sup>. Ethnomedical leads and subsequent ethnopharmacological studies discovered many plant-derived drugs used in modern medicine. There are more than 100 drugs of known structure that are extracted from higher plants and used in allopathic medicine. Botanicals serve humans as source of valuable chemicals. In today's US \$ 300 billion global pharmaceutical market, approximately 25% of all prescriptions contain active agents originally derived from plants.

Phytomedicines have three distinct advantages 1) Botanical extracts can be directly evaluated without initial chemical isolation for clinical efficacy 2) Increased solubility / bioavailability in crude forms 3) Synergy between different active constituents.

### **Migraine: Clinical Manifestations and Therapies**

Migraine is characterized by attacks of intense pulsatile and throbbing headache, typically unilateral in nature with or without aura. Attacks are episodic and, by their very nature resolve with time. Associated symptoms, such as nausea, vomiting and heightened sensitivity to light (photophobia), and sound (phonophobia) may occur during the headache phase.

The headache phase may be preceded by symptoms, such as mood fluctuations and gastrointestinal disturbances. A minority of patients experience a more specific sensory

disturbance prior to the headache, called 'aura' which usually has visual disturbances. Migraine affects a substantial fraction (10-20 %) of world population (more women than men).

With regard to the pathophysiology of migraine, several theories have been proposed; the major three, proposed till date, are vasodilatory (due to cerebral vasodilatation), neurological (abnormal neurological firing) and neurogenic dural inflammation mechanism (release of inflammatory neuropeptides). The objective of today's acute migraine therapy is to reverse the vasodilatation in the intracranial, extracerebral vessels and thereby abolish pain.

The drugs used for the treatment of migraine can be divided into two groups: agents that abolish the acute migraine headache and agents aimed at its prevention. In the last decade there has been a tremendous progress in the acute migraine therapy, with sumatriptan, belonging to a new class of drugs, known as 5-HT<sub>1B/1D</sub> receptor agonists, providing the lead<sup>5,6</sup>. The success of sumatriptan, which is a gold standard in migraine therapy, stirred up a research interest in the field of migraine. These agents have changed the lives of countless patients with migraine. Currently prophylactic treatments for migraine include calcium channel blockers, 5-HT<sub>2</sub> receptor antagonists, beta adrenoceptor blockers and  $\gamma$ -amino butyric acid (GABA) agonists, etc<sup>7,8</sup>. Unfortunately, many of these treatments are non specific and not always effective<sup>8</sup>. Perhaps due to the involvement of multiple receptors, the ergot alkaloids are associated with a number of side effects including nausea and vomiting, gangrene and myocardial infarction. The disadvantages of the triptans are their high cost and the restrictions on their use in the presence of cardiovascular diseases.

Phytomedicine has offered an alternative source of therapy for migraine sufferers, and provided some additional information about the pathogenesis of migraine<sup>9, 10</sup>. Feverfew (*Tanacetum parthenium*) and Butter bur (*Petasites hybridus*) are some of the plants that have been used for centuries for migraine relief<sup>11, 12</sup>.

### **The herbal approach for the treatment of migraine**

The exploitation of plants for medicines has a long and honorable history. It was also linked with the initial development of the science of pharmacology, which used natural products to elucidate physiological process. The pharmacological evaluation of natural products therefore forms an intrinsic part of pharmacognosy, one of the original disciplines of the pharmaceutical profession.

Natural products are the basis of many standard drugs used in modern medicine, namely digoxin, hyoscine, theophylline, ergometrine, pilocarpine, vincristine and vinblastine. Plant compounds have also served as templates for the development of many drugs, including local anesthetics such as lignocaine from cocaine; analgesics and cough suppressants developed from opiates etc. Some of the important developments are taxol from Pacific Yew, *Taxus brevifolia* and artemisinin from *Artemisia annua*. Garlic, an ancient remedy, is one now showing its true potential as an antisclerotic and antithrombotic. Plant drugs also serve efficient treatments for some conditions where 'conventional' medicine has little to offer, such as liver damage, where lignans from *Silibum marianum* can prevent fatalities by death cap mushroom (*Amanita phalloides*) poisoning and infectious hepatitis.

During the last few decades, there has been a resurgence of interest in plants as sources of medicines and of novel molecules for use in the elucidation of physiological/biochemical phenomena. There is a worldwide 'green' revolution, which is reflected in the belief that herbal remedies are safer and less damaging to the human body than synthetic drugs. Laboratories around the world are engaged in the screening of the plants for biological activity with therapeutic potential. One major criterion for the selection of a plant for such study is traditional healers' claim for its therapeutic usefulness<sup>13</sup>.

The clinical applications of taxol, etoposide and artemisinin have boosted the interest in higher plants as sources of new drugs<sup>14</sup>. Despite the belief that majority of clinical drugs are synthetic in origin, it is interesting to note that 6 out of 20 pharmaceutical prescription drugs dispensed in last decade were natural products and over 50% of top 20 drugs could be linked to natural product research<sup>14</sup>. There still remains an urgent need to develop new clinical drugs and this can be exemplified by the numerous diseases which result from the malfunction of the central nervous system e.g. Alzheimers and Parkinson's disease, epilepsy, migraine, pain, schizophrenia and sleeping disorders as well as other life threatening challenges like AIDS and various types of cancer<sup>15</sup>.

#### ***Feverfew (*Tanacetum parthenium*)***

Leaves or infusions of feverfew, a short bushy perennial herb widely distributed in UK, have long been used as a folk remedy for fever, arthritis and migraine. One of the active ingredients, parthenolide in feverfew is the sesquiterpene lactone parthenolide a compound that has shown inhibitory effects on serotonin release and platelet aggregation *in vitro*<sup>11, 6, 17</sup>. Also feverfew reportedly inhibits the synthesis of 5-lipoxygenase, leukotrienes, prostaglandins and thromboxanes that mediate inflammation<sup>18</sup>. Clinical

trials appear to indicate that feverfew taken prophylactically has beneficial effects in patients who suffer from migraine<sup>19, 20</sup>.

There were four trials conducted to evaluate the efficacy of feverfew in patients with migraine. One of the four trials conducted with feverfew in a self-selected group of feverfew users showed that withdrawing feverfew led to a statistically significant increase in headache frequency<sup>19</sup>. A pilot study of 17 A pilot study of 17 patients with migraines were given capsules of freeze dried feverfew leaves or placebo daily. Those who received placebo had a tripling in the frequency of migraine attacks.. The placebo group had a tripling in the frequency of migraine attacks. Patients on placebo reported increased nervousness, tension headaches, insomnia, or joint stiffness, constituting a post feverfew syndrome. The other conventional trial was conducted in a larger group of patients with migraine, most of whom (71%) had never used feverfew<sup>20</sup>. This trial reported a smaller difference between feverfew and the control treatment, but still found the difference to be statistically significant, in favor of feverfew. The third trial was a double blind, randomized crossover study that tested the efficacy of feverfew compared with placebo, concluding that the treatment with feverfew was associated with a significant reduction in pain intensity and associated symptoms (nausea, vomiting, photophobia and phonophobia)<sup>21</sup>. The fourth study found an insignificant difference between feverfew given as an alcoholic extract and placebo for reducing migraine frequency<sup>22</sup>.

A double-blind study which evaluated the dose response of stable feverfew extract (MIG-99) at three dose levels (2.08, 6.25 and 18.75 mg three times a day). The results indicated



that the frequency of the attacks are reduced in a dose dependent manner. However, the extract failed to exhibit any migraine prophylactic effect in general<sup>23</sup>

The same formulation has been reevaluated at the dose of 6.25 mg three times in a placebo controlled parallel-group study. The results showed a statistically significant and clinically relevant difference between MIG-99 and placebo regarding the reduction of migraine frequency. The intention-to-treat analysis yielded a decrease in migraine attacks by 1.9 attacks per month by MIG-99 when baseline covariables are taken into account. It has been suggested that MIG-99 represented an effective prophylactic migraine therapy<sup>24</sup>. Limited information indicates that adverse events were no more common with feverfew than with the placebo treatment<sup>23,24</sup>. Feverfew's side effects included mouth ulceration and a more widespread oral inflammation associated with loss of taste. Feverfew's mechanism of action is uncertain. It is rich in sesquiterpene lactones, especially parthenolide, which may be a non-specific NE, 5-HT, bradykinin, prostaglandin and acetylcholine antagonist. The biological variation in the sesquiterpene lactone content and the long-term safety and effectiveness of feverfew are of concern<sup>19</sup>.

Until recently it was generally assumed that parthenolides represent the active principle of feverfew. This hypothesis was supported by *in vitro* experiments that emphasized its biological activity. The studies have demonstrated that the plant has inhibitory effects on platelet aggregation and release of serotonin from blood platelets and leucocytes<sup>25,26</sup>. One trial that used feverfew extract with a standardized and constant concentration of parthenolides to treat migraine did not show any beneficial effect<sup>22</sup>. In a more recent report, parthenolide has been studied in nitroglycerin induced Fos activation. In this study feverfew extract with different concentrations of parthenolide and purified parthenolide

are tested on nitroglycerin induced changes in the rat brain. Parthenolide exhibited inhibitory activity upon a subgroup of brain nuclei in response to nitroglycerin administration. The results of the study suggest that parthenolide is the component responsible for the biological activity of feverfew<sup>27</sup>.

Feverfew is available in capsule, tablet and liquid extract forms. All the feverfew preparations are standardized to contain 0.2% of parthenolide.

***Butterbur (Petasites hybridus)***

Butterbur is a perennial shrub found throughout Europe as well as parts of Asia and North America. It has been traditionally used for treating cough, asthma and skin wounds. Currently the primary therapeutic uses of Butterbur are prophylactic treatment of migraine and as an antispasmodic agent. The extract of the rhizomes of *Petasites hybridus* and its constituents, petasine and isopetasine are shown to exhibit strong vasodilatory activity on smooth muscle preparations, comparable to papaverine<sup>28</sup>. Moreover, the components of Butterbur are found to possess anti-inflammatory activity through the inhibition of leukotriene synthesis<sup>12</sup>. Recent in vitro study, the extract of butterbur exhibited direct- and lipopolysaccharide induced - inhibition of COX-2 and thus the release of prostaglandin E2 (PGE2) in primary rat microglial cells. Furthermore, the extract prevented the LPS-induced activation of p42/44 mitogen activated protein kinase activation in the same cell lines<sup>29</sup>. Intravenous administration of iso-S-petasin produced dose-dependent hypotensive and bradycardiac responses in anesthetized rats. Iso-S-petasin, also attenuated the Ca<sup>2+</sup> induced contractions in depolarized rat aorta. Studies in cultured vascular smooth muscle cells revealed that iso-S-petasin possesses L-type

voltage dependent calcium channel antagonistic activity<sup>30</sup>. These findings serve as the pharmacological basis for the prophylactic treatment of migraine with Butterbur.

In a double-blind placebo controlled clinical study *Petasites hybridus* extract (Petadolex) or placebo was administered at a dosage of 2 capsules (25 mg each) twice a day for 12 weeks. The results of the study demonstrated that Petadolex is effective in the prophylactic treatment of migraine. The extract reduced the frequency of attacks by a maximum of 60% as compared to baseline<sup>31</sup>. More recently, a number of studies with various doses of *Petasites* extract have been reported. In a three arm parallel group study 75 mg and 50 mg doses (twice a day) of the extract are studied with placebo for 4 months. The 75 mg and 50 mg doses reduced the attack frequency by 48 % and 36 % while only 26 % observed in the placebo group<sup>32, 33</sup>. In yet another multi-center open label study *Petasite* extract was studied in children and adolescents at doses of 50 and 150 mg per day for 4 months. The extract showed reduction in attack frequencies and the treatment was well tolerated in children and teenagers<sup>34</sup>. Safety data from clinical trials, postmarketing surveillance and pharmacovigilence suggest Butterbur extract is safe in the treatment in human<sup>35</sup>.

**Reetha (*Sapindus trifoliatus*),**

*Sapindus trifoliatus* Linn. family Sapindaceae is medium sized deciduous tree found in south India. High content of saponins and sugars have been reported in the pericarp. In the folklore literature, fruits are reported to possess emetic, tonic, astringent and anthelmintic properties and are used in the treatment of asthma, colic due to indigestion, diarrhoea, cholera, tubercular glands, paralysis of the limbs and lumbago. A thick watery solution of the pulpy mesocarp is introduced into the nose of the patient for relief in

hemicrania and for restoring consciousness during epileptic and hysteric fits. Further, fruits of *Sapindus trifoliatus* have been scientifically investigated for their anti-pruritic, anti-spermatogenic, anti-androgenic and spermicidal properties<sup>37-40</sup>.

Recently, *Sapindus trifoliatus* has been investigated in various *in vitro* and *in vivo* models of nociception, migraine and inflammation. The aqueous extract of *Sapindus trifoliatus* (ST), exhibited affinity towards, 5-HT<sub>2B</sub> receptors in an isolated rat fundus assay. However, ST did not exhibit affinities towards acute migraine targets (viz. 5-HT<sub>1B/1D</sub> receptors and  $\alpha$ -adrenoceptors) in experiments conducted in various *in vitro* tissues<sup>41</sup>. At moderately high concentrations, ST inhibited the serotonin release from human platelets<sup>41</sup>. ST exhibited anti-nociceptive activity in various central and peripheral pain models<sup>42</sup>. ST exhibited analgesic activity in hyperalgesic pain models predictive of *in vivo* migraine models<sup>43</sup>. Data obtained from *in vitro* and *in vivo* studies on various inflammatory models suggest that ST has anti-edematogenic activity in acute models of inflammation<sup>44</sup>. Studies on behavioral and neurological animal models revealed the dopaminergic and serotonergic modulatory role of ST<sup>45,46</sup>. However, so far no human trials have been reported with the use of *Sapindus trifoliatus*.

A wealth of literature lends to support the use of several herbal medicines in the treatment of migraine and other types of headache. Cannabis (*Cannabis sativa*), Ginger (*Zingiber officinale*) and Sweet bay (*Laurus nobilis*) are not to be excluded from the list<sup>9,10, 47, 48</sup>. More specifically, there is an recent upsurge in the use of cannabis in the treatment of migraine. Anandamide, the endogenous ligand of cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors, was able to inhibit neurogenic dural vasodilatation, CGRP-, capsaicin-, and NO-induced dural vessel dilation in the rat intravital microscopy model of

trigeminovascular activation. The CB<sub>1</sub> receptor antagonist AM251 was able to reverse the above anandamide mediated inhibition. It was speculated that anandamide may tonically inhibit neuronal firing in the trigeminovascular system<sup>49</sup>.

### **Concluding Remarks**

The unmet needs of antimigraine therapy still exists as migraine is a disorder with variety of complex etiologies. It remains the hope of research scientists that in the not too distant future we shall see a new class of antimigraine drugs arising from the understanding molecular pathophysiology of migraine in the post-triptan era. Currently feverfew is the only herbal, which is extensively used in the prophylactic treatment of migraine. However, the proof-of-concept clinical studies are awaited with interest for the potential use of butterbur and *Sapindus trifoliatus* for the treatment of migraine. The data from the studies of *Petasites hybridus* and *Sapindus trifoliatus* support the ethno-medical application of these plants in the treatment of migraine (hemicrania) and provide new hope for the development of novel ethno-leads towards the pharmacotherapy of migraine.

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