Introduction
Preface

The development of traditional medical systems incorporating plants as a means of therapy can be traced back to the Middle Paleolithic age some 60,000 years ago. Ethnomedicine, which may be defined broadly as the use of plants by humans as medicines, is a highly diversified approach to drug discovery that involves observation, description, and experimental investigation (screening) for possible biological/medicinal properties from indigenous drugs. It is based on botany, chemistry, biochemistry, pharmacology, physiology and other disciplines such as anthropology, archeology and history that contribute to the discovery of natural products with medicinal activity (Rivier L, Bruhn J. 1979, Editorial. J. Ethn. 1). Ethnopharmacology has come to stay as interdisciplinary scientific exploration of biologically active agents, traditionally observed in man (Dahanukar et al, 2000). Ethnomedical leads and subsequent ethnopharmacological studies developed 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. Furthermore, well over 60% of the new chemical products registered by the FDA as anticancer agents, antimigraine agents and antihypertensive agents are natural products or derivatives thereof in the time frame of 1981-2002.

Natural products have been the traditional pathfinder compounds with an untold diversity of chemical structures unparalleled and unmatched even by the largest combinatorial libraries.

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, and 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 designing 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 health care practices like Ayurveda, Siddha and Unani. These medical practices originated from times immemorial and developed gradually, to a large extent, by relying or based on practical experiences without significant references to modern scientific principles (Subramonium and Pushpangadan, 1999; Dahanukar et. al, 2000). Use of plants as a source of medicine has been inherited and is an important component of the health care system in India. In the Indian system of medicine, most practitioners formulate and dispense their own recipes; hence this requires proper documentation and research. According to the World Health Organization, more than 60% of the World’s population use ethnomedicine as part of their primary health care. In western world also, the use of herbal medicines is steadily
growing with approximately 40% of the population reporting use of herb 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 (Dubey et al 2004; Seth and Sharma, 2004). 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 use provides the source to study the specific plant species with potential to be used in a particular disease. Hence, a systemic approach through experimental and clinical validation of efficacy is required for a plant identified for traditional medicine, as is done in modern medicine (Seth and Sharma, 2004). Although herbal medicines are effective in treatment of various ailments, very often these drugs are unscientifically exploited and/or improperly used. A detailed pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable herbal drugs for many dreaded diseases.

Botanicals have served 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

- Botanical extracts can be directly evaluated without initial chemical isolation for clinical efficacy
- Increased solubility / bioavailability in crude forms
- Synergy between different active constituents
Thus the emerging scenario of widespread usage and therapeutic potential of phytomedicines prompted us to investigate a phytomedicine as a potential therapy to treat migraine.

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 experiences 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 a market size of approximately US$ 2-3 billion.

With regard to the mechanisms of migraine and its pathophysiology, several theories have been established; major three, proposed till date are vasodilatory (due to cerebral vasodilation), neurological (abnormal neurological firing) and neurogenic dural inflammation (release of inflammatory neuropeptides).

The objective of today’s acute migraine therapy is to reverse the vasodilation in the intracranial, extracerebral vessels and thereby abolish pain.

The drugs used in the treatment of migraine can be divided in to 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 therapy of migraine, with sumatriptan belonging to a new class of drugs, now known as 5-HT\textsubscript{1B/1D} receptor agonists, providing the lead (Humphrey et al 1988 & 1990). The success of sumatriptan, which is a gold standard in
migraine therapy, stirred up the 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$_2$ receptor antagonists, beta adrenoceptor blockers and y- amino butyric acid (GABA) agonists etc. (Amrey, Rogers et al, 2000). Unfortunately, many of these treatments are non specific and not always effective (Goadsby, 1997). Despite such progress, in view of the complexity of the etiology of migraine, it still remains undiagnosed and available therapies are underused. Thus, there exists an imperative need towards an effective antimigraine therapy, which has fewer side effects. The need could be explored either from synthetic or natural / herbal origin.

Phytomedicine has offered alternative source of therapy for migraine sufferers, and provided some additional information about the pathogenesis of migraine (Russo, 1992; Gorji,2003). Feverfew (Tanacetam parthenium) and Butterbur (Petasites hybridus) are some of the plants that have been used for centuries for relief of migraine (Groenewegen and Heptinstall, 1990; Grossmann and Schmidramsl, 2001).

Thus in light of the above facts and with a backdrop of the unmet needs of antimigraine therapy (in spite of the availability of triptans which are not free from Cardiovascular side effects), migraine research is beginning to be focused on the development of novel agents for the acute/prophylactic treatment. The present study has been planned to investigate the antimigraine potential of herbal source (Sapindus trifoliatus).
Objectives of the present study
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*Sapindus trifoliatus* Linn. Belonging to Sapindaceae family is a medium sized deciduous tree commonly found in the southern part of India. The pericarp of the fruit has been reported to contain relatively high content of saponins identified as pentacyclic triterpene hederagenin glycosides. The pericarp is reported to possess various medicinal properties such as emetic, astringent and anti-paralytic\(^1\). Aqueous solution of the pulpy mesocarp is instilled in to the nose of the patients suffering from migraine and epilepsy\(^2\).

During our ongoing search for the active principles from traditional medicine of plant origin we come across a herbal preparation which was being dispensed by an Ayurvedic Practitioner for the treatment of migraine. The preparation essentially consisted of an aqueous extract of the pericarp of *Sapindus trifoliatus* popularly known as Reetha in Hindi. The mode of the treatment was by intranasal administration of the above aqueous extract. Till now no pharmacological especially antimigraine activity has been reported for *Sapindus trifoliatus* and no active principles have been isolated. Since *Sapindus trifoliatus* extract was clinically used as a folklore medicine in the treatment of migraine the present investigation was undertaken to validate the scientific basis of antimigraine activity.

The aims and objectives of the present study are as follows:

- To prepare aqueous extract of *Sapindus trifoliatus*.
- To develop parameters for standardization of raw material (pericarp) and the aqueous extract of *Sapindus trifoliatus* using latest techniques like HPLC, HPTLC etc.
- To carry out bioassay directed fractionation of aqueous extract of *Sapindus trifoliatus*.
- To isolate pure compounds from aqueous extract of *Sapindus trifoliatus*.
To characterize the pure compounds isolated from aqueous extract of *Sapindus trifoliatus*.

**Resources**
