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Migraine: Molecular Basis and Herbal Medicine

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1. Introduction

Migraine is a common and disabling brain disorder with no single characteristic which could be used for a definite diagnosis. Usually a combination of different presentations is used as diagnostic criteria which may lead to a challenging feature of under- or misdiagnosis and also under-treatment. Diagnostic criteria for migraine usually emphasize on specificity compared to sensitivity which enhances their research values but reduces their clinical worth. The criteria are subjective and the lack of objective tests to confirm migraine diagnosis raises the need of rule out of other diagnoses. For this reason a potential diagnostic biomarker for migraine would certainly find wide application and may improve current severe deficiencies in migraine diagnosis.

1.1 Definition and classification

The term migraine is originated from Greek word *"hemicrania"* (Silberstein, 2004), meaning "one side of the head". Migraine headache as an episodic neurovascular phenomenon is characterized by recurrent attacks of unilateral headache (Silberstein, 2004) while headache is recognized as the most well-known symptom of migraine, its origin generally remains unclear (Messlinger, 2009). A combination of genetic and environmental factors contributes to the onset, progression, and severity of headache (Pietrobon & Striessnig, 2003). Migraine is classified into two major types — *migraine without aura* and *migraine with aura* (ICHD, 2004).

1.1.1 Migraine without aura

Migraine without aura (previously known as hemicrania simplex, common migraine) is a specific neurological disorder characterized by unilateral, pulsating quality, aggravation on movement, and moderate to severe headache, nausea and photophobia. Most migraineurs suffer from this subtype of migraine, and there are higher frequency and more severe attacks in comparison with migraine with aura. Owing to strong relationship between migraine without aura with menstrual cycle, the menstrual migraine (i.e. pure menstrual migraine and menstrually-related migraine) is categorized in this subtype. In pure menstrual migraine in

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contrast to other types, migraine headaches are strictly restricted to the perimenstrual phase and do not happen at other times of the menstrual cycle (ICHD, 2004).

1.1.2 Migraine with aura

Migraine with aura (formerly known as classical migraine, ophthalmic, hemiplegic migraine) is defined as a recurrent disorder involving headache attacks appearing gradually over 5-20 minutes and lasting for less than 60 minutes. The aura encompasses focal neurological symptoms that precede or accompany at the onset of migraine attacks. Aura can involve reversible visual and sensory symptoms and speech weakness. Inherited forms of familial hemiplegic migraine and sporadic hemiplegic migraine, in which patients suffer from motor weakness, are classified in this subtype (ICHD, 2004).

1.2 Epidemiology and burden of health

The worldwide prevalence of headache for all age-group is considered to be more than 47%, and of migraine is 10.3% (Jensen & Stovner, 2008). In the United States around 6% of men and 18% of women experience at least one migraine attack in a given year. Before puberty, there is generally no sex difference (Jensen & Stovner, 2008), but incidence rate generally increases with age, especially in girls, until mid-puberty and then declines (Jensen & Stovner, 2008; Silberstein, 2004). In different ethnicity Europeans have the higher incidence rate followed by African-Americans and Asian-Americans (Silberstein, 2004).

It is obvious that migraine has a severe negative influence on quality of life (Silberstein, 2004). Because of its impact on health status, migraine is ranked as one of the top 20 causes of healthy life lost and disability by World Health Organization (WHO) (ICHD, 2004). Migraine annual cost for employers is about 13$ billion in the USA. Direct annual medical cost is over 1$ billion (Silberstein, 2004).

1.3 Comorbidity

In medicine, comorbidity describes the presence of one or more separate conditions that exists simultaneously in the same individuals (Jensen & Stovner, 2008; Scher et al., 2005). In general, the current global prevalence of tension-type headache in patients with migraine is 94%, of which 56% suffer frequent episodic tension-type headache (Jensen & Stovner, 2008). There is a growing evidence for a link between migraine and other diseases, including stroke, hypertension, diabetes, asthma, and obesity (Jensen & Stovner, 2008), as well as epilepsy (Scher et al., 2005). It is noted that migraine has been related to various indefinite disorders such as fibromyalgia, non-headache pain (lower back pain or local muscle pain) (Jensen & Stovner, 2008), some congenital heart defects like patent foramen ovalea, anxiety, and depression (Scher et al., 2005).

2. Molecular basis

2.1 Pathogenesis

Migraine was once considered to be a vascular phenomenon resulting from intracranial vasoconstriction and rebound vasodilation. However, recently it has been suggested that neurogenic process leads to a vascular change and consecutive alteration in cerebral

perfusion (neurovascular theory) (Pietrobon & Striessnig, 2003). Historically Ebn-e-sina *(Avicenna,* 980–1037*)* was actually the first medical scientist who addressed neurovascular theory of migraine in the *Canon of Medicine*, which was published centuries ago. It seems that this fact has been ignored in recent articles considering history of theories of pathogenesis of migraine (Abokrysha, 2009).

Although the underlying cause of migraines has remained unknown, many biological events have been associated with migraine attacks. A potential cause of migraine is any change in the stability of pathways either directly or via trigeminocervical pain system. This could be inherited as a low activation threshold.

Cortical spreading depression is another theory that could result in aura by a spreading wave of depolarization (Lauritzen M, 1994). Aura is accompanied with a localized decrease followed by an increase in blood flow in parieto-occipital cortex (Charles, 2009) which leads to activation followed by depression of neurological activity over a cortical area. It could result in the release of some inflammatory mediators that irritates cranial nerves root, mostly the trigeminal nerve that transmits the sense of face and most of the head. There are some experiments supporting involvement of cortical event in the initiation of headache as well (Bartleson & Cutrer, 2010).

Migraine has a strong (up to 50%) genetic component, which is higher in migraine with aura than migraine without aura, with a probable multifactorial polygenic inheritance. Genetic load can be considered as a determinant that is modulated by external and internal factors (migraine triggers) (Pietrobon & Striessnig, 2003). Also, it has been reported that not only genes are involved in migraine, but also their protein encoded by them and their metabolites (known as biomarkers) may be important in its etiology (Loder, 2006).

2.2 Biomarkers in migraine

2.2.1 Definition and classification

Biological markers (biomarkers) have been defined as biological characteristics that can be objectively measured and evaluated as the indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Mayeux, 2004).

It has been shown that changes in the level of some molecules, arising from deficiency, increase or impairments of regulatory processes in their production pathway might be associated with etiology of migraine. Although, it is unknown that these changes can result from or/result in migraine.

In migraine, different biomarkers including genetic, and/or biochemical have been used for diagnosis and/or study of the pathophysiology of the disorder. The term of biomarkers in migraine can be classified in two different categories. Biomarkers of exposure or "antecedent biomarkers" (such as genetic biomarkers) defined as factors that exist before the development of migraine. The levels of these biomarkers are linked to increase or decrease in migraine susceptibility. On the contrary, biomarkers of disease can be defined as factors, used as the indicators of the presence or development of migraine. They can be used to screen the individuals with migraine and prediction of treatment response. In addition, the biomarkers in migraine can be classified into groups, based on the types of measured markers, such as genes, proteins and metabolites patterns in various body fluids (Loder, 2006). According to these categories, all genetic, and proteomic and metabolomic biomarkers are discussed later.

2.2.2 Genetic biomarkers

They are defined as genetic variations (mutations or polymorphisms) that can predict disease susceptibility, and help in early diagnosis of migraine, course of disease, disease severity and/or response to therapy. Some mutations that were found to be related with hemiplegic migraine (de Vries et al., 2006, 2009), and common migraine (Lafrenière et al., 2010), are good examples of mutation biomarkers. Some polymorphisms were also found to be more valuable for screening patients with higher susceptibility into migraine attack in the future (De Vries et al., 2006).

2.2.2.1 The mutation biomarkers in migraine

2.2.2.1.1 Hemiplegic migraine

Apart from familiarity—i.e., no affected relatives vs. affected first degree or second-degree relative(s), familial hemiplegic migraine is comparable in diagnostic criteria to sporadic hemiplegic migraine (Russell & Ducros, 2011).

2.2.2.1.1.1 Familial hemiplegic migraine

The familial hemiplegic migraine phenotype is associated with autosomal dominant mutations in the *CACNA1A*, *ATP1A2* and *SCN1A* genes. These familial forms of migraine caused by mutations in these genes are referred to FHM1, FHM2, and FHM3, respectively (de Vries et al., 2009; Russell & Ducros, 2011). *CACNA1A* gene is located on 19p13 and encodes the main subunit of $Ca_v2.1$ neuronal channels. Most of these mutations are missense which account for 50-75% of mutations in FHM families (De Vries et al., 2006). The *CACNA1A* T666M mutation is the most frequent cause of familial hemiplegic migraine. Interestingly, *CACNA1A* mutations are also found in other disease, such as episodic ataxia type 2 (EA-2) and spinocerebellar ataxia type 6 (SCA-6) (De Vries et al., 2006).

The *ATP1A2* gene is located on 1q23. This gene encodes the α2 subunit of sodium-potassium pumps. Several diseases such as basilar-type migraine and common migraine are associated with mutations in the *ATP1A2* gene (de Vries et al., 2006; 2009).

The *SCN1A* gene is located on 2q24 and encodes the α1 subunit of the neuronal voltage-gated sodium channel $Na_v1.1$. It is suggested that Mutations in this gene account for generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI) (de Vries et al., 2006; 2009).

Recently it has been shown that mutation in the *SLC1A3*, encoding the glial glutamate transporter EAAT1 is responsible for pure hemiplegic migraine. Also, a homozygous deletion in *SLC4A4*, encoding the electrogenic sodium bicarbonate (Na^+–HCO^{3-}) cotransporter NBCe1 was associated with familial hemiplegic migraine. *SLC1A3* and *SLC4A4* seem to be the fourth and fifth genes (FHM4 and FHM5) which are involved in familial hemiplegic migraine (Russell & Ducros, 2011).

Functional studies have shown that FHM mutations cause (i) an enhancement of Ca^{2+} influx via $Ca_v2.1$ channels leading to an enhanced release of glutamate, at least in the cortex (in the case of *CACNA1A* mutations), (ii) a dysfunction in glial uptake of K^+ and glutamate from the synaptic cleft (in the case of *ATP1A2* mutations), and (iii) an enhanced recovery from fast inactivation and in that way an increased firing rate of

neurons (in the case of *SCN1A* mutations). Therefore, as mentioned above, an increase of extracellular glutamate and K^+ levels in the synaptic cleft is associated with FHM mutations. Neurons may depolarize in a more straightforward manner to facilitate cortical spreading depression (de Vries et al., 2006; 2009). It could well explain the aura in these monogenic subtypes (de Vries et al., 2009). The findings in FHM support that dysfunction in ion transport is a crucial factor in migraine pathophysiology and might facilitate the identification of molecular pathways involved in migraine (de Vries et al., 2006; 2009).

2.2.2.1.1.2 Sporadic hemiplegic migraine

Sporadic cases of hemiplegic migraine can result from a de-novo mutation in genes related to the FHMs or by inheritance of a gene mutation from an asymptomatic parent (due to incomplete penetrance) (Russell & Ducros, 2011).

Up to now, only a few *CACNA1A* and *ATP1A2* mutations have been reported in patients with the sporadic hemiplegic migraine. For that reason, it is suggested that these genes have negligible role in pure sporadic hemiplegic migraine. A comparable nomenclature with familial hemiplegic migraine is also used for sporadic hemiplegic migraine, too. Accordingly, mutations in the *CACNA1A* and *ATP1A2* genes are referred to as sporadic hemiplegic migraine (SHM1 and SHM2, respectively) (Russell & Ducros, 2011).

2.2.2.1.2 Common migraine

Contrary to hemiplegic migraine, common forms of migraine are a genetically complex disorder with higher prevalence, genetic and phenotypic heterogeneity. Like other complex genetic traits, finding responsible genes are much more difficult (de Vries et al., 2006). Despite these problems and absence of any evidence of association between genes encoding the ion channels and common migraine in previous studies (Nyholt et al., 2008), it has been reported recently that there is a strong genetic link to common forms of migraine (Lafrenière et al., 2010). Using a candidate gene approach and functional analysis, researchers have identified a mutation, F139wfsX24, in the gene encoding the two-pore domain potassium channel TRESK (TWIK-related spinal cord potassium channel) *KCNK18* in the patients with migraine with aura. The TRESK is involved in pain pathways and regulates neuronal excitability. The mutation can lead to a complete loss of channel function (Lafrenière et al., 2010) and for the first time, a common form of migraine is linked to a genetic mutation (Wood, 2010). The agonist-promoted up-regulation of TRESK activity can act as a beneficial treatment option, either as an acute therapy or as a long-term preventive approach for individuals with migraine (Lafrenière et al., 2010).

Recently, in a genome-wide association study, evidence for association of common forms of migraine and rs1835740 on chromosome 8q22.1 has been reported. It has been claimed that this is the first relationship between genetic and common forms of migraine, particularly migraine with aura. This allele, is located between astrocyte elevated gene 1 (*MTDH/AEG-1)* and plasma glutamate carboxypeptidase (*PGCP*). Due to the role of these two genes in glutamate homeostasis, it seems that complementary pathways such as the glutamate system could fasten mendelian channelopathies with pathogenesis of common forms of migraine (Anttila et al., 2010).

2.2.2.2 Polymorphisms in migraine

Many positive associations have been reported in different linkage studies between common forms of migraine and polymorphisms. However, these results mainly have not been replicated, and are therefore of less clinical value (de Vries et al., 2006; 2009). Methylenetetrahydrofolate reductase gene *MTHFR* 677C>T polymorphism and angiotensin I-converting enzyme *ACE* D/I polymorphism are two good examples for genetic association with migraine. Methylenetetrahydrofolate reductase is a key enzyme in folate and homocysteine metabolism and angiotensin-converting enzyme is an exopeptidase that catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor (Colson et al., 2006).

A meta-analysis study has shown that the *MTHFR* 677TT genotype was associated with increased risk of migraine with aura and *ACE* II genotype is protective against both migraines with and without aura. Due to high heterogeneity among studies, both variants appeared to be correlated with common forms of migraine only among non-Caucasian populations (Schürks et al., 2010). However, further studies may be required among other ethnicities. Previously it has been shown that *ACE* and *MTHFR* genes act synergistically as a genetic risk of migraine and having at least one copy of the *ACE* D allele beside the *MTHFR* TT genotype increases the risk of migraine with aura by ~3 fold (Roda, 2005).

Another meta-analysis study about serotonin transporter gene (5-HTT) variants (including 5-HTTLPR, VNTR and SNP) indicates that only the VNTR polymorphism is associated with an increased risk of migraine (Liu et al., 2011). Existing evidences indicate that the genetic polymorphisms in serotonergic system, dopaminergic system, gamma amino butyric acid receptor system, inflammation related genes (de Vries et al., 2009), inducible nitric oxide synthase promoter (Jia et al., 2011), hypocretin-1 (also termed orexin-A) receptor (Rainero et al., 2011), and Notch 3 gene (G684A variant) (Menon et al., 2010) are associated with an increased risk of migraine. Other studies suggest that some haplotypes related to endothelial nitric oxide synthase (Gonçalves et al., 2011) and vascular endothelial growth factor (Gonçalves et al., 2010) could affect the susceptibility to migraine. So genotyping of only one polymorphism might not be sufficient and haplotype analysis may be needed to elucidate the association between migraine and these polymorphisms. Future studies with larger sample sizes will be necessary to confirm the present results.

2.2.3 Proteomic and metabolomic biomarkers

Principally, the global analysis of metabolites (metabolomics) and proteins (proteomics) in body fluids and tissues can provide certain advantages in understanding the underlying mechanisms of migraine. The proteomic and metabolomic signature, mostly belong to biochemical markers (such as proteins, peptides, amino acids, and amines), can identify a putative disease fingerprint for migraine in blood, urine and cerebrospinal fluid (Loder, 2006). The list of these biomarkers has been discussed in several reviews (Edvinsson, 2006; Harrington, 2006; Loder et al, 2006).

2.2.3.1 Calcitonin gene-related peptide

Calcitonin gene related peptide is a 37-amino acid neuropeptide that is a member of the *calcitonin* family of peptide. Calcitonin gene related peptide plays an important role in the

modulation of physiological functions such as regulation of vascular tone and modulation of pain perception (Durham, 2006; Fischer, 2010).

Calcitonin gene related peptide was originally thought to contribute to migraine and elevated level of this peptide has been reported in this disease (Arulmani et al. 2004; Durham, 2006; Fischer, 2010). Calcitonin gene related peptide can lead to enhancement of cerebral circulation, transmission of pain-related impulses and neurogenic inflammation (Durham, 2006). In fact, in the endothelium dependent and independent (binding to its receptors on the smooth muscle cells) pathways, calcitonin gene related peptide activates adenylate cyclase and enhanced cyclic adenosine mono phosphate production is believed to be involved in increase of blood circulation. Moreover, the cyclic adenosine mono phosphate production can cause enhancement of nitric oxide synthase activity and nitric oxide production followed by increase in cyclic guanosine mono phosphate production as a secondary messenger for nitric oxide. The enhancement of cyclic guanosine mono phosphate production was connected to vasodilation and increase in cerebral circulation (Arulmani et al., 2004). It is believed that the effects of calcitonin gene related peptide on enhancement of substance P release and excitatory amino acids such as glutamate play an important role in transmission of calcitonin gene related peptide- mediated pain impulses. Also, it seems that calcitonin gene related peptide - mediated neurogenic inflammation is followed by degranulation of mast cells and the release of inflammatory agents (Durham, 2006).

2.2.3.2 Serotonin

Serotonin or 5-hydroxytryptamine is synthesized from tryptophan, in various tissues including brain (Hamel, 2007). Additionally, this molecule could be found in some plants (Badria, 2002). The fluctuations of platelet and plasma level of 5-hydroxytryptamine (Panconesi, 2008), change in lymphoblastic serotonin level (Nagata et al., 2007) and number of 5-hydroxytryptamine platelet transporters (as indirect index of 5-hydroxytryptamine recovery) (Panconesi, 2008) have been reported in patients with migraine. There are some controversies regarding the role of serotonin in migraine. It has been shown that there are the gender and seasonal variations of serotonin neurotransmission in human such as 5-hydroxytryptamine receptor hypersensitivity and its decreased cerebrospinal fluid level in women and 5-hydroxytryptamine receptor hyposensitivity in summer. On the other hand, the higher frequency of migraine in women and higher frequency of its attacks in summer compared with winter and autumn has been reported in most studies. Also, nowadays, the triptan, a selective serotonin 5-hydroxytryptamine ($1_B/1_C$) agonist is being used in the treatment of acute migraine attacks. In spite of controversial results about mentioned issues, the importance of the failure of a serotonergic system in migraine pathogenesis is significant. Accordingly, the serotonin system is considered to be involved in migraine (Panconesi, 2008). Moreover, additional studies are necessary to establish its importance in migraine etiology.

2.2.3.3 Melatonin

The synthesis of melatonin or N-acetyl-5-methyoxytryptamine from serotonin occurs in the pineal gland and other tissues in humans (Pandi-Perumal et al., 2006). In addition to the vertebrates, this indnole amine has been identified in numerous taxa including bacteria, unicellular eukaryotes (Hardeland et al., 2011; Pandi-Perumal et al., 2006) and plants (Ansari

et al., 2010; Chen et al., 2003). In vertebrates, the production of melatonin reaches to its peak in the darkness and the light inhibits its secretion. Also, age-related decreases in melatonin synthesis and secretion have been reported (Pandi-Perumal et al., 2006). Most studies indicate that melatonin may play a significant role in sleep and circadian rhythm regulation, improvement of immune system (Hardeland et al., 2011) and antioxidant activity (Tan et al., 2007).

It has been found that plasma and urinary levels of melatonin (Peres et al., 2006) and nocturnal urinary 6-sulfatoxymelatonin concentration (Masruha et al., 2008) decrease in patients with migraine. Melatonin receptors are present in trigeminal ganglion and trigeminal nucleus of mammals that could explain its action. Also trigeminovascular nociception that is induced by cortical spreading depression in rats is attenuated by melatonin (Ambriz-Tututi et al., 2009). Therefore, melatonin has been suggested as a possible biomarker for migraine (Loder et al., 2006) and there is a great potential for using melatonin in acute or prophylactic treatment of migraine headache (Miano et al., 2008; Peres et al., 2004). Melatonin seems to be related with migraine pathogenesis in many ways, including its anti-inflammatory and antioxidant effects such as reduction in pro-inflammatory factors and scavenging toxic free radicals, potentiation of gamma amino butyric acid and opioid analgesia, suppression of nitric oxide synthase activity, inhibition of dopamine release, protection against glutamate neurotoxicity, and regulation of neurovascular regulation (Peres, 2005; Peres et al., 2007).

2.2.3.4 Nitric oxide

Nitric oxide as a diatomic molecule is synthesized by nitric oxide synthases from L-arginine. Changes in plasma and platelet (Gallai et al., 1996) levels of nitric oxide in migraine sufferers have been shown. Abnormalities in nitric oxide signaling pathway and increase in activity of nitric oxide synthase has been shown to be associated with enhanced susceptibility to migraine (Olesen, 2008). The oral administration of nitroglycerin as a nitric oxide donor induces headaches, which resembles to spontaneous migraine attacks. Also, in migraineurs, nitroglycerine inhibitors attenuated these nitroglycerin-induced attacks (Olesen, 2008) and as a result nitric oxide is suggested as fundamental biomarker for migraine (Loder et al., 2006). According to this point of view, nitric oxide is thought to be central in the pathophysiology of migraines. It seems likely that nitric oxide functions as the modulator of cellular toxicity, inflammatory responses, release of calcitonin gene related peptides as a potent peptide vasodilator, platelet function, endothelium-dependent vasodilatation, and transmission of pain impulses (Olesen, 2008).

2.2.3.5 Cations

Although, elements have been excluded from metabolome and proteome subclass, their strong connection with biomarkers cannot be ignored. The cations play a key role in cerebrospinal fluid functions and change in their serum levels is associated with pathogenesis of several diseases such as migraine headache (Donma & Donma, 2002). Considering the role of mutation in sodium, calcium and sodium-potassium channels in familial hemiplegic migraine, cations are important in migraine pathogenesis (Harrington et al., 2006). Moreover, nowadays, calcium channel blocker drugs are being used in migraine treatment, more extensively (Goadsby & Sprenger, 2010).

It seems that magnesium has a greater role as a possible biomarker of migraine, than other elements (Loder et al., 2006). It has been reported that serum magnesium concentration decreases in patients with migraine (Roudbari et al., 2005; Sun-Edelstein & Mauskop, 2009). Clearly, decreased magnesium concentration can trigger migraine attack (Mauskop, 1998), probably by promoting cortical spreading depression; alteration in neurotransmitter release and platelet hyperaggregation (Sun-Edelstein & Mauskop, 2009). The blockage of serotonin receptor and/or inducible receptor of glutamate, NMDA, and inhibition of synthesis and release of nitric oxide are believed to be of great physiological importance of magnesium (Sun-Edelstein & Mauskop, 2011).

According to the results of a study, increase in cerebrospinal fluid sodium concentration, independently from other clinical or pharmacological fluctuations of other cations, can participate in pathogenesis of migraine with aura. It is probable that concomitant elevated sodium concentration and normal cerebrospinal fluid potassium concentration, partially can decrease resting membrane potential and lead to decrease of action potential threshold in patients with migraine (Harrington et al., 2006). It has been suggested that salt out acts as potential migraine trigger (Brainard, 1976).

2.2.3.6 Others

Despite the importance of mentioned biomarkers in migraine pathology, several studies have reported changes in level of other biochemical biomarkers such as S100β, a glia-derived cytokine (Papandreou, 2005), dopamine and dopaminergic system (Charbit et al., 2010), endothelin-1 (Kallela et al., 1998), excitatory neurotransmitters such as glutamate and substance P, and pain-related molecules such as met-enkephalin and β-endorphin (Harrington, 2006) in/or between migraine attacks.

2.2.4 Practical considerations

There are some notable issues about mentioned biomarkers: (i) several of these biomarkers have potential interactions with others and have influences on concentration of other biomarkers. For example, melatonin as an imperative antioxidant is considered to be scavenger of nitric oxide and its toxic metabolite peroxynitrite ($ONOO^-$) from body. Additionally, melatonin can indirectly lead to decrease in nitric oxide synthase activity and expression in body (Acuña-Castroviejo et al., 2005); (ii) Results of measurement of a biomarker from two separate samples can be different. For example the concentration of melatonin in urine of patients with migraine is more valuable than its plasma concentration. As a result, assessment of concentration of urine and plasma melatonin were considered as confirmed and probable biomarker, respectively (Loder et al., 2006), and (iii) the levels of some these biomarkers in each person or in each attack are not varied similarly, therefore it seems that contemporary investigation of proteome or metabolome profile in migrainous patients, as has been employed for other conditions such as cancer (Casado-Vela et al., 2011), is necessary.

Despite of wide-ranging list of migraine biomarkers which has been described; it is believed that a complete assessment of clinical features and signs, and careful history taking may be decisive in the migraine diagnosis and these biomarkers, mainly genetic ones, "will be a test, not the mere identification of a marker, which will change clinical practice."(Goadsby, 2006). Nevertheless, migraine symptoms appeared to vary not only in each person but also in each

attack. It is noted that after taking a medical history from a patient, one should be sure about absence of any other common headache in this context. To support this diagnosis, a series complementary tests including genetic and biochemical markers appears to be useful. Also, nowadays, instead of treatment of migraine based on pathological mechanisms, it is focused on clinical symptoms. It is evident that current treatments relieve migraine attacks slowly. Treatment strategies based on biomarkers can help us in this field. For example, if a biomarker reaches to normal level or diminishes, it is possible that the choice of the strategy for treatment is successful and/or the patients don't require further treatments. In addition, the investigation about cause of changes in biomarker levels can help us to explore mechanism and underlying environmental factors that trigger migraine. Also, it can be helpful in differentiation of migraine diagnosis (Loder, 2006).

2.3 Trigger factors in migraine

Any factor, that on exposure or withdrawal, alone or in combination, leads to the development of an acute migraine headache, is known as migraine trigger (V.T. Martin & Behbehani, 2001). They also are called precipitating or provoking factors that usually happen before the attack by less than 48 hours (P.R. Martin, 2010). These triggers can be categorized into two identifiable groups: internal and external (V.T. Martin & Behbehani, 2001). Based on twin studies, observed concordance rate for migraine headache in mono- and dizygotic twins are 37-52% and 15-21%, respectively. The fact that concordance rate for migraine in monozygotic twins is not 100%, suggests that environmental factors contribute to the development of migraine headache (V.T. Martin & Behbehani, 2001).

2.3.1 External triggers

External triggers that we hear most often about them, can be classified broadly as environmental, behavioral, dietary, chemical, allergens and some drugs (V.T. Martin & Behbehani, 2001) of which some are listed in Table 1. Stress is the most commonly mentioned migraine trigger, and it seems that can initiate or augment frequency and severity of migraine attack (Hauge et al., 2009; Millichap & Yee, 2003). Most information about prevalence of triggers has been reported in population- or clinical- based studies in a self-report manner by patients own experience which could lead to a significant bias. These studies didn't have the technical or methodological strength and the results are variable and contradictory (P.R. Martin, 2010; V.T. Martin & Behbehani, 2001) and more discussion about the epidemiological studies on external triggers are not necessary, as well.

2.3.1.1 Possible mechanisms

An understanding of the aura and headache components of migraine provides a basis for the potential mechanism of action of dietary triggers. Theoretically, migraine triggers could influence on the cerebral cortex, organizations innervated by the terminal nerve (i.e. dural arteries), the trigeminal pain pathway (trigeminal nerve, thalamic nuclei), and regulatory pathway within the brain stem or the limbic system contribute to migraine. Therefore, migraine triggers aggravate migraine headache in a number of diverse ways, including: (i) direct effect on excitatory or inhibitory neuroreceptors; (ii) release of internal neuropeptides or neurotransmitters and nitric oxide; and (iii) direct excitation of neurons (V.T. Martin & Behbehani, 2001; Millichap & Yee, 2003).

Dietary[a]	Environmental[b]
• Caffeinated beverages	• Bright light/visual stimuli
• Alcoholic beverages	• Odors/smells
• Aged cheeses	• Weather changes
• Chocolate	• Cigarette smoke
• Coffee, tea, cola	Behavioral[b]
• Chocolate	• Stress/tension
• Food allergens (Dairy products, yogurt)	• Hunger/not eating
• Ice cream	• Emotions
Chemical[a]	• Lack of sleep and Sleeping late/excess
• Monosodium glutamate	• Fatigue/tiredness
• Tyramine	• Exercise
• Nitrates	• Hair wash or head bath[c]
• Artificial sweetener (Aspartame)	Minor head trauma[d]

[a](V.T. Martin & Behbehani, 2001; Millichap & Yee, 2003); [b](P.R. Martin, 2010; V.T. Martin & Behbehani, 2001); [c] Reported in Indian patients (Ravishankar, 2006), [d] Frequently reported as a trigger for hemiplegic migraine (Russell & Ducros, 2011)

Table 1. External Trigger Factors in Migraine.

2.3.2 Internal triggers

Internal triggers are those that occur in our body. The most common internal triggers are sex hormones (neurosteroids and ovarian steroids). The key stages of reproduction including first menstruation, pregnancy and menopause are associated with frequency or severity of migraine. It is suggested that sex steroids (i.e. estradiol and progesterone) have a central role in migraine etiology (Gupta et al., 2007; V.T. Martin & Behbehani, 2006b) especially in menstrual migraine. 35-51% of female migraineurs have menstrually related migraine, even though 7-19% has pure menstrual migraine. Interestingly only attacks of migraine without aura occur during the perimenstrual time period and attacks of migraine with aura happen equally during the menstrual cycle. The main trigger of menstrual migraine seems to be withdrawal of estrogen rather than the maintenance of continuous high or low estrogen levels. On the other hand, sustained changes in estrogen levels related to pregnancy (augmented levels) and menopause (declined levels) likewise affect headaches (V.T. Martin & Behbehani, 2006b).

2.3.2.1 Possible mechanisms

The neurosteroids and ovarian steroids may exert their effects on vascular and nervous system via cytosolic and nuclear receptors (genomic pathway) and membrane receptors (non-genomic pathway) and initiate a migraine attack (V.T. Martin & Behbehani, 2006a). These steroids can lead to neuronal excitation via increase in calcium and decrease in magnesium concentration, vasodilatation and activation of trigeminal nerve through synthesis and release of nitric oxide, neuropeptides (i.e. calcitonin gene related peptide), increase or decrease in inhibitory or excitatory neurotransmitters synthesis and opioids and their impacts on receptors. However there are some contradictory results of negative or positive effects of steroids on onset of migraine attack (Gupta et al., 2007; V.T. Martin & Behbehani, 2006a).

2.3.3 Genetic background

Any change in activity of involved gene in hormonal and vascular function causes increase in susceptibility to migraine. Recently, it has been suggested that the association between migraine and dysfunction of genes involved in progesterone and/or estrogen receptor 1, might play a role in increased susceptibility to migraine (Colson et al., 2006). Moreover, diamine oxidase activity in histamine breakdown in the intestine might be important in those who are sensitive to food containing histamine. It seems that vitamin B6 supplementation enhances diamineoxidase activity, and in that way decreases histamine-induced migraine attacks (Ross, 2011).

3. Treatment

Introducing the concept of brain disorder in migraine etiology led to a new approach in treatment options in migraine disorder (Monteith & Goadsby, 2011). Migraine treatment can be classified into medical and non-medical treatment. Non-medical treatments include patient education and behavioral therapy for the prevention of trigger factors involved in migraine. The pharmacotherapy for migraine can be categorized into preventive drugs, which are administrated daily regardless of the presence of headache and acute drugs, which are taken by patients immediately after symptoms appearing (Goadsby et al, 2002).

3.1 Drugs

Acute treatment is classified into nonspecific treatments, including non-steroidal anti-inflammatory drugs (NSAIDs), and migraine-specific treatments, including ergot derivatives and the triptans (Table 2) (Goadsby et al, 2002). However, only one third of patients in clinical trials feel pain-free 2 hours after taking a triptan orally, so novel treatment options are still required. Recently, new drugs have been developed by targeting neural sites. Interestingly, safety and efficiency of some of these drugs have been confirmed in phase II and some other in phase III clinical trials (Monteith & Goadsby, 2011).

Preventive therapy (prophylaxis) including beta-blockers, anticonvulsants like valproate and topiramate, and calcium channel blockers are preferred choice for treatment of patients unresponsive to acute-attack medications (Table 2). In the U.S, therapeutic guidelines regular migraine prophylaxis for patients with more than two acute attacks per week are recommended, but in the Europe the regular preventive treatment therapeutic guidelines are recommended on the basis of two or more acute attacks per month (Goadsby & Sprenger, 2010).

3.2 Complementary alternative medicine

Despite some controversy regarding formal definition for Complementary Alternative Medicine, the National Center for Complementary and Alternative Medicine, defines it as “a group of diverse products, medical and health care systems, practices that are not presently considered to be part of conventional medicine.” Using complementary alternative medicine along with conventional medical treatments as part of a multidisciplinary treatment strategy has higher probability to result in appropriate responses. Although, some evidences are available in favor of these treatments, more extensive studies are required to fully elucidate their efficacies (Sun-Edelstein & Mauskop, 2011). Here nutritional supplements and medicinal herbs will be explained further.

Acute attack drugs in migraine[a]
Specific drugs
• Ergot derivatives
• (ergotamine and dihydroergotamine)
• Serotonin 5-HT receptor agonists
• 5-$HT_{1B/1D}$ receptor agonists
• Triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, Sumatriptan, and zolmitriptan.
• Serotonin 5-HT_{1F} receptor agonists*
• Other receptors antagonists*
• Calcitonin gene-related peptide (Olcegepant and telcagepant)
• Glutamate AMPA/kainate
• Transient receptor potential vanilloid-1
• Prostanoid EP4
• Inducible and neuronal nitric oxide synthase inhibitors*
Nonspecific drugs
• Non-steroidal anti-inflammatory drugs (Aspirin, acetaminophen),
• Opiates, and combination analgesics
Preventive drugs in migraine[b]
• Beta-blockers (Propranolol, Metoprolol)
• Anticonvulsants (Valproate, Topiramate)
• Calcium channel blockers (Flunarizine)
• Antidepressants (dosulepin (dothiepin), Venlafaxine)
• Serotonin antagonists (Pizotifen, Methysergide)
• ACE inhibitors (Lisinopril, Candesartan)
• Cortical spreading depression inhibitors (tonabersat) *
• Neuromodulators (the stimulation of the greater occipital nerve) *
• Botulinum toxin type-A*
• Patent foramen ovale closure*

* These drugs are under investigation in phase II or III clinical trial. [a](Goadsby et al., 2002; Goadsby & Sprenger, 2010; Monteith & Goadsby, 2011); [b](Goadsby & Sprenger, 2010).

Table 2. Acute and preventive drugs for migraine treatment.

3.2.1 Riboflavin

Riboflavin (vitamin B_2) is critical for membrane stability, cellular energy production and the maintenance of cellular functions (Rios & Passe, 2004; Sun-Edelstein & Mauskop, 2009). It is thought a deficit in brain mitochondrial energy reserve, causes biochemical changes that trigger the trigeminovascular system, and therefore play an important role in migraine attacks (Rios & Passe, 2004). Riboflavin can increase the mitochondrial energy efficiency. It is reported an attenuation of the frequency of migraine attack after supplementation with high dose riboflavin (400 mg/day) for three months (Sun-Edelstein & Mauskop, 2009) (Rios & Passe, 2004). Despite minor side effects of high-dose of riboflavin (including diarrhea and polyuria), no identified complication is reported for riboflavin in pregnancy (Rios & Passe, 2004). However, there is no consensus that riboflavin is to significantly operative in migraine preventive.

3.2.2 Coenzyme Q10

Due to its function on mitochondrial respiratory chain and antioxidant activity, it seems to be helpful to prevent migraine (Sun-Edelstein & Mauskop, 2009; 2011). Moreover, efficacy of coenzyme Q10 supplementation in migraine pediatric prophylaxis has been reported (Ross, 2011; Sun-Edelstein & Mauskop, 2009; 2011) and approximately 300 mg of coenzyme Q10 is thought to be effective in migraine prevention (Sun-Edelstein & Mauskop, 2009). However, these results require further approval before to be suggested as an effective treatment.

3.2.3 Alpha-lipoic acid

Similar to riboflavin and coenzyme Q10, alpha-lipoic acid improves oxygen metabolism in mitochondria and adenosine triphosphate production (Sun-Edelstein & Mauskop, 2011). Although no defined supplementation dose for alpha-lipoic acid have been approved by the U.S Food and Drug Administration, it is reported that supplementation with 600 mg of alpha-lipoic acid once a day for three months attenuated the frequency of migraine attacks (Sun-Edelstein & Mauskop, 2009).

3.2.4 Magnesium

Based on results of several investigations, failure in calcium-magnesium balance in patients with migraine plays a key role in pathogenesis of this disease. In addition to possible role of magnesium as a biomarker for migraine (described previously), regarding its physiological functions in energy production, maintaining blood vessel tone and stability of neurons, it may be beneficial in patients with migraine (Ross, 2011; Sun-Edelstein & Mauskop, 2009; 2011). Although oral magnesium can prevent migraine attacks and intravenous magnesium can reduce acute headache, the use of magnesium has shown controversial results (Sun-Edelstein & Mauskop, 2009; 2011). The daily supplementation with 400 mg of chelated magnesium (Sun-Edelstein & Mauskop, 2009), magnesium oxide or 600 mg of trimagnesium dicitrate (Rios & Passe, 2004) is thought to be effective in treatment of migraine. These remarks have not been confirmed yet. The high dose of magnesium can cause diarrhea, loss of appetite, nausea, vomiting and gastric irritation. Also, owing due to involvement of high dose of magnesium in decreasing fluoroquinolones absorption, it is not recommended for patients with ulcerative colitis, diverticulitis, or renal failure and in pregnant or nursing women (Rios & Passe, 2004).

3.2.5 Dietary avoidance

Elimination of food allergens (including cow's milk; wheat; eggs) (Ross, 2011) or dietary triggers (described in external triggers previously) (V.T Martin & Behbehani, 2001; Millichap & Yee, 2003), which initiate a migraine attack, can lead to elimination or reduction of frequency and severity of migraine attacks. Thus, they can be considered as candidate for treatment of migraine. Though, due to daily need to some of the mentioned foods for cellular function, it is impossible to eliminate them from dietary completely, so they are replaced with either (Millichap & Yee, 2003).

4. Herbal medicine

4.1 History

Before the advent of modern synthetic drugs, herbs were considered as first choice for treatment of human diseases. In spite of the fact that using herbs has been diminished in modern medicine, fortunately, there is a growing trend, particularly in migraine disorder. There have been few studies examining herbal remedy effectiveness and most of our information is based on traditional experiences. However, mechanism of action of many of them have not been fully understood.

In traditional medicine in Iran, China and India and some older societies, factors such as geographic location and experience in the proven effectiveness of herbs, affect their acceptance as medicine. The famous scientists gathered their ancestor's experiences and their own researches which remained as useful references for the future. *Qanoon fel teb* (*The Canon of Medicine*) by Ebn-e-Sina *(Avicenna,* 980–1037), *al-hawi* (*Continens*) by Zakariya Râzi (Rhazes, 860–940) and *Kitab-al-Maliki* (*Liber Regius*) by Ali Ebn Al-Abbas-al-Majusi (Haly Abbas, 949–982) are good examples in this regard (Gorji, 2003; Gorji & Khaleghi Ghadiri, 2002). On the other hand, using new techniques to analyze the active ingredients of plants and methods for the study of underlying mechanism, can confirm their effectiveness and safety. Due to the easier and faster access to medical information resources of traditional medicine for treatment, as well as new technology in various countries to identify the mechanism of action of herbal ingredients, it is possible to clarify more aspects of mechanism underlying treatment of several diseases, such as migraine.

4.2 Herbs application for migraine treatment

4.2.1 Analgesic effects

Analgesics are widely used for pain relief worldwide. Many herbal remedies have been proved to be effective in painful situations like migraine headache empirically and/or in clinical trials. Some of these botanical analgesics which have shown pain killing effects are listed in Table 3 (Yarnell, 2002; Zareba, 2009; Zengion & Yarnell, 2011). Although some aspects of herbs mechanism of action have been understood, more studies are required to elucidate anodyne herb's function.

Herbs containing salicylates and those with anti-inflammatory effects are usually safe and beneficial for pains caused by inflammation (Yarnell, 2002; Zareba, 2009; Zengion & Yarnell, 2011). *Salix alba* is a good example which decreases pain due to its salicin content and is reported for migraine treatment (Gorji, 2003; Gorji & Khaleghi Ghadiri, 2002). Feverfew and ginger (Mustafa & Srivastava, 1990) are two important anti-inflammatory herbs with proved anti-migraine activity. Hypnotic anodynes have more general analgesic properties and are ideal when pain contributes to insomnia. Some studies recommended Valerian to be used in migraine treatment. Numerous centrally-acting herbs have stronger analgesic effect and they should be used with lower doses to avoid adverse effects. Topically used herbs like *Capsicum frutescens* could propose a useful way to relieve neuropathic pain, and other pain syndromes due to capsaicin as an effective component. Intranasal application of capsaicin for relief of migraine is reported (Yarnell, 2002).

Anti-inflammatory herbs	**Salicylate-containing herbs**
• *Curcuma Longa* (Turmeric)	• *Salix alba* (White Willow)*
• *Angelica sinensis* (Dang Gui, Tang Kui, Dong Kuai),	• *Populus tremuloides* (Quaking Aspen)
• *Harpagophytum procumbens* (Devil's Claw)*	**Topical herbs**
• *Boswellia serrata* (Frankincense)*	• *Capsicum frutescens* (Cayenne)*
• *Zingiber officinalis* (Ginger)*	• *Urtica dioica* (Stinging Nettle)
• *Tanacetum parthenium* (Feverfew)*	• *Symphytum officinale* (Comfrey)
Centrally-acting herbs	**Miscellaneous**
• *Cannabis sativa* (Cannabis)*	• *Ginkgo biloba* (Ginkgo)*
• *Hypericum perforatum* (St. John's Wort)*	• *Centella asiatica* (Gotu Kola)
• *Corydalis yanhusuo*	• *Viburnum opulus* (Cramp Bark)
• *Bryonia alba* (White Bryony)	• *Viburnum prunifolium* (Black Haw)
Hypnotic herbs	• *Scutellaria laterifolia* (Skullcap)
• *Valeriana officianalis* (Valerian)*	• *Scutellaria baicalensis* (Huang qin)
• *Piscidia piscipula, P. erythrina* (Jamaican Dogwood)	• *Rosa canina**
• *Eschscholtzia californica* (California Poppy)	• *Solidago chilensis* (Brazilian Arnica)

* analgesic herbs which are traditionally used for relief of migraine headache (Gorji, 2003; Gorji & Khaleghi Ghadiri, 2002; Yarnell, 2002; Zareba, 2009)..

Table 3. Analgesic herbs used for pain relief (Yarnell, 2002; Zareba, 2009; Zengion & Yarnell, 2011).

4.2.2 Prophylactic effects

Efficacy for prophylactic drugs is defined as a reduction in migraine frequency of more than 50%. Also it could refer to reduction in attack severity, or significant reductions in nausea, vomiting, photophobia and phonophobia. Feverfew and butterbur were the first herbs that have been utilized for migraine preventive therapy.

4.2.2.1 Feverfew

Although, feverfew (*Tanacetum parthenium*) is a perennial herb native to Balkan Mountains in Eastern Europe, in more recent times it has become naturalized widely in Europe, North America, and South America (Sun-Edelstein & Mauskop, 2011). Several studies have been reported that feverfew has anti-inflammatory and anti-platelet aggregation properties, thereby having promising results in the treatment of migraine (Rios & Passe, 2004; Ross, 2011). Its anti-migraine action is probably related to its active compound i.e. parthenolide (Sun-Edelstein & Mauskop, 2011). Although optimal supplementation dose have not been established, daily supplementation with 100 mg (Sun-Edelstein & Mauskop, 2009) or 50-145 mg of feverfew supplements, containing at least 0.2% parthenolide (Rios & Passe, 2004; Ross, 2011) is thought to be effective in migraine treatment. The usage of these doses is associated with side effects like nausea, and diarrhea, mouth ulcerations (only when chewing leaves), and withdrawal symptoms including muscle stiffness, anxiety, and rebound migraine headache. It is noted that the use of feverfew supplements is not

recommended in pregnancy (due to uterus contraction), nursing women, children below 2 years, patients with high sensitivity to plants of *Asteraceae* family (Rios & Passe, 2004; Ross, 2011), and patients undergoing surgery, due to its function as an inhibitor of platelet aggregation (Ross, 2011).Using feverfew as an approved medication require further investigations.

4.2.2.2 Butterbur

Butterbur (*Petasites hybridus*) also known as pestwurz, blatterdock, bog rhubarb, and butter-dock (Rios & Passe, 2004), is an herb, found throughout Europe and parts of Asia (Sun-Edelstein & Mauskop, 2011). It seems to be a promising drug for reduction of frequency and severity of migraine attacks (Rios & Passe, 2004; Ross, 2011), especially in children (Oelkers-Ax, et al., 2008). Butterbur is rich in pharmacologically active compounds called sesquiterpenes; such as petasin and isopetasin (Sun-Edelstein & Mauskop, 2011). Despite uncertainty about its optimal dose, similar to feverfew, by Food and Drug Administration (Rios & Passe, 2004), 75 mg of butterbar twice daily for a month, following 50 mg twice a day (Sun-Edelstein & Mauskop, 2009) or 50-100 mg twice a day, containing at least 7 mg of petasin and isopetasin (Rios & Passe, 2004*)* is believed to be beneficial for migraine headaches. So, until performing further studies, it cannot be supported as an effective treatment for migraine. Pyrrolizidine alkaloids found in butterbur are recognized as toxins with carcinogenic and hepatotoxic effects. For this reason, it is necessary to eliminate these alkaloids from commercial butterbur extracts (Sun-Edelstein & Mauskop, 2011). It is not recommended for the pregnant or nursing mothers (Rios & Passe, 2004).

4.2.2.3 MigriHeal®

Recently a novel herbal remedy was introduced with prophylactic effect against migraine attacks which lasts even after the discontinuation of therapy (Fallah et al., 2005). This herbal drug which is used as inhalation up to 4 months can decrease headache frequency and severity (www.araamesh.com). No adverse effects were reported by patients and animal study proved its safety even in higher doses. Investigating the effect of M*igriHeal*® extracts on nitric oxide production in mouse endothelial cell-line showed reduced production in a dose-dependent manner (Ansari et al., 2005; 2007).

4.3 Possible mechanisms of medicinal herbs used in migraine

On the contrary to primary products, such as carbohydrates, lipids, proteins, heme, chlorophyll, and nucleic acids, which participate in modulation of cellular metabolism and maintenance of plant cells, the benefits of phytomedicine typically may be caused by the combined action of secondary plant compounds. Although, up to now, there are some *in vivo* and *in vitro* studies about role of phytomedicine in migraine treatment as well as its possible mechanism, further investigation is required. Therefore, studies exploring the effect of phytomedicine on frequency and severity of migraine attacks can help us to understand the etiology of migraine. Besides, investigation of plant derivatives can lead to new drugs for migraine treatment.

Here, we discuss possible mechanisms of several medicinal plants, used in migraine headache treatment.

4.3.1 Compensatory components

Due to high level of some molecules in medicinal plants, which are reduced in patients with migraine, it seems that they can be used as compensatory mechanism for migraine treatment. It has been shown that some medicinal plants including *Tripleurospermum disciforme*, *Viola odorata* and *Tanacetum parthenium* used in treatment of migraine headache, contain high concentration of melatonin (Ansari et al., 2010). Notably, these results are in line with other studies about other medicinal plants used in treatment of neurologic disorders, *Tanacetum parthenium*, *Hypericum perforatum*, and *Scutellaria biacalensis* (Murch et al., 1997) and Chinese medicinal plants are used in treatment oxidative abnormality-related diseases (Chen et al., 2003). Plasma level of melatonin is decreased in migraine and its therapeutic use in this disorder has been reported (Peres et al., 2006). In the other hand, owing to increase in plasma concentration of melatonin in human (Oba et al., 2008) and rat (Reiter et al., 2005) following phytomelatonin administration, the high content of melatonin (from picograms to micrograms per gram of plant material) in these medicinal plants is thought to be responsible of reduction of migraine attack and can be considered as potential candidate for migraine prevention.

Interestingly, *In vivo* studies have been shown that extract of some medicinal plants can enhance gene expression and activity of enzyme involved in melatonin synthesis, N-acetyltransferase, thereby increasing melatonin level (Qu et al., 2008). In addition, it seems that the extract of some plants has large affinity for the serotonin (5-HT_{4e}, 5-HT_6, and 5-HT_7) and melatonin (ML1 and ML2) receptors (Abourashed et al., 2004). In spite of some discrepancies between the studies on role of enzymes involved in melatonin synthesis and melatonin receptors in migraine etiology, the involvement of melatonin in migraine pathogenesis is notable. Accordingly, further studies are required to elucidate possible impact of medicinal plants on reduction or treatment of migraine attacks as well as underlying mechanism.

In addition of melatonin, high level of several metabolites of tryptophan metabolism including 5-Hydroxytryptophan, as a direct precursor of the neurotransmitter serotonin, (used to boost levels of this compound in the human brain thereby treating cases of serotonin deficiency syndrome) (Lemaire & Adosraku., 2002), tryptamine and serotonin (Badria, 2002) have been considered in some medicinal plants. It seems that the metabolites will be a potent term in phytomedicine research reports, particularly in migraine treatment.

4.3.2 Effects on signaling and expression regulation

4.3.2.1 Effects on nitric oxide formation and calcitonin gene related peptide

These effects can result from elimination of nitric oxide, inhibition of gene expression of enzymes and removal of calcium ion from environment and its influence on calcium channels and calcitonin gene related peptide. For example, some medicinal plants such as Lavender, Coriander, Chamomile and Viola can decrease nitric oxide as stated in Ansari et al. report. There have been noted that different forms (e.g. aqueous extract, essential oil) of these herbs significantly suppress nitric oxide production in a dose-dependent manner (Ansari et al., 2005; 2007) and possibly thereby reducing migraine attacks. These herbs with analgesic and/or prophylactic effects are also summarized in Gorji et al. reviews (Gorji, 2003; Gorji & Khaleghi Ghadiri, 2002).

It is believed that the parthenolide as a sesquiterpene lactone in feverfew prevents migraine. The parthenolide has been found to inhibit, lipopolysaccharide-induced nitric oxide formation and lipopolysaccharide-induced activation of the inducible isoform of nitric oxide synthase. It should be noted that several flavonoid glycosides in feverfew have shown vasodilation and anti-inflammatory properties, but parthenolide in other plants have not shown anti-migraine effects. Interestingly, extract with high parthenolide showed a low tolerability, in comparison with purified parthenolide.

Treatment of rat trigeminal ganglia cultures with *Theobroma cacao* extract, following exposure to depolarizing stimuli was shown to block calcium channel activity and to inhibit the HCl and capsain-stimulated enhancement in calcitonin gene related peptide secretion. According to in vivo study, this extract was demonstrated to decrease nitric oxide release and inflammatory cytokines from macrophages significantly (Abbey et al., 2008). Nutritional coca in a similar manner, can suppress calcitonin gene related peptide expression in neurons and inducible nitric oxide synthase activity, thereby it is involved in migraine pathophysiology, pain feeling and inflammation-related responses. Interestingly, cocoa can suppress neuronal increased expression of the mitogen-activated protein kinase p38 and extracellular signal-regulated kinases after stimulation with acute or chronic peripheral inflammation (Cady & Durham, 2010). It is noted that mitogen-activated protein kinase signal transduction participated in initiation and stimulation of inflammatory responses and pain feeling. It has been suggested that high level of borocyanides in *Arace catechu* as well as inhibitory influence on inducible nitric oxide synthase activity can be involved in its underlying mechanism in anti-migraine properties (Bhandare et al., 2011).

4.3.2.2 Effects on Arachidonic pathway

The feverfew (parthenolide) is known to inhibit prostaglandin, thromboxane B4 and leukotriene B_4 release by phospholipase A_2 inhibition (Summer et al., 1992). Main active ingredients of butterbur are petasin and isopetasin, inhibiting both lipoxygenase pathway and leukotriene synthesis –related anti-inflammatory effects (Rios & Passe, 2004; Ross, 2011). On the other hand, the inhibitory properties of ginger in prostaglandins, thromboxanes and leukotriene have been linked to its anti-migraine effects (Mustafa & Srivastava, 1990).

4.3.2.3 Effects on platelet activity

Regarding to decrease in platelet 5-hydroxytryptamine content, change in 5-hydroxytryptamine transport as well as platelet cytosolic free-calcium concentration, in patients with migraine, it is evident that abnormalities in platelet function may participate in migraine pathogenesis (Rogers et al., 2001). According to results of a study, for quantification of the antiplatelet effect of Australian plants extracts via testing adenosine di phosphate induced platelet aggregation and the release of 5-hydroxytryptamine, it has been demonstrated that these extracts through regulation of cyclooxygenase pathway may contribute to inhibition of platelet 5-hydroxytryptamine release (Rogers et al., 2000). Previously, Rogers et al reported that *E. vespertilio* and *C. ambiguous* can be served as traditional treatments for headache due to inhibitory effect of their extracts on platelet activation (Rogers et al., 2001).

In view of the several studies about function of gingkolide B (an herbal constituent extract from *Ginko biloba* leaves) as a natural antiplatelet activating factor, recently it has been shown that its administration can be effective in patients with primary headache (Usai et al., 2011). Based on investigation of ginsenosides (active constituent of *Genus Panax*, ginseng) effects on rats, it has been shown that they inhibit thrombin or collagen-induced platelet aggregation. In addition, it has been reported that enough concentrations of allicin, a primary constituent of garlic (*Allium sativum*) can result into platelet aggregation and degranulation blockage. Despite of in vitro studies, it is noted that after administration of these plants in healthy individuals, the platelet function does not change (Beckert et al., 2007).

On the other hand, goshoyoto as an herbal drug seems to be effective in treatment of migraine headaches by suppression of platelet aggregation. Its two herbal components, zingiberis and evodiae, have been shown to inhibit collagen-induced platelet aggregation. Interestingly, 6-gingerol and 6-shogaol as two constituents of zingiberis can inhibit platelet aggregation by inhibition of cyclooxygenase-1 activity (Hibino et al., 2008). In another study, anti-migraine properties of *Sapindustrifoliatus* water extract has been linked to both inhibition of 5-HT_{2B} receptor and release of platelet serotonin (Arulmozhi et al., 2004).

4.3.2.4 Effects on ion channels

Evidences link the ion channel gene mutations, particularly those encoding voltage-gated calcium channels, to rare and severe hemiplegic migraine. Accordingly, use of L-type voltage-gated calcium channels blockers for the prophylactic relief of migraine seems occasionally reasonable. Studies show that extracts of *E. bignoniiflora*, *A. symphyocarpa* and *E. vespertilio* have potential antagonists of neuronal voltage- gated calcium channels (Rogers et al., 2002). In addition, due to combined effects of $Ca_v2.1$-inhibitory properties of petasins (as the main constituents of the anti-migraine herb *P. hybridus*) and sulfur containing petasins in these herbs, it can be considered as appropriate approach to migraine prophylaxis (Horak et al., 2009). These findings prompt further electrophysiological studies to investigate the modulatory capacity of these compounds on other ion channels implicated in hemiplegic migraine pathophysiology.

4.3.2.5 Others

In addition to mentioned mechanism underlying the effect of herbal medicine in migraine treatments, several pathways is thought to be involved in this regard. For example, based on results of one study (Arulmozhi et al., 2005), it has been suggested that the high level of saponin in *Sapindus trifoliatus* can have a regulatory role in dopaminergic and adrenergic receptors. Also, anti-inflammatory, analgesic and narcotic properties of this herb can be responsible for its effects in migraine treatment. It is worth mentioning that these receptors can associate with migraine pathogenesis.

5. Conclusion

It seems that future researches should be emphasized to unravel the hidden area of migraine pathophysiology using metabolomics and proteomics study which could also lead to find some biomarkers to discriminate patient and healthy people. The latter could be used in new classification of the disease, and also as a strong diagnostic tool.

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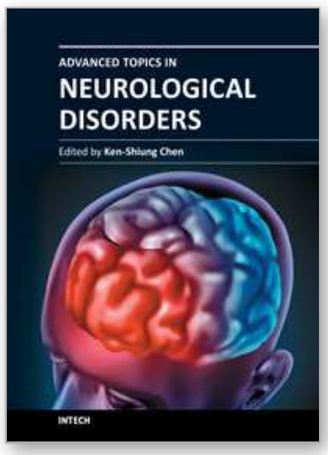

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This book presents recent advances in the field of Neurological disorders research. It consists of 9 chapters encompassing a wide range of areas including bioengineering, stem cell transplantation, gene therapy, proteomic analysis, alternative treatment and neuropsychiatry analysis. It highlights the development of multiple discipline approaches in neurological researches. The book brings together leading researchers in neurological disorders and it presents an essential reference for researchers working in the neurological disorders, as well as for students and industrial users who are interested in current developments in neurological researches.

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