

The Effects of *Curcuma domestica*, *Zingiber officinale* and Magnesium for Migraine Prophylaxis

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Abstract

In the US and worldwide, the prevalence of migraines is increasing. Migraines are considered to be a severely disabling condition. Migraines can onset due to noxious stimuli inducing flaccidity of the vasculature for 24-48 hours. There are a number of mechanisms that may be responsible. However, the most prominent are irregularities of the trigeminovascular system, a platelet disorder, serotonin deficiency and mitochondrial dysfunction. The addition of *Curcuma domestica* or *Zingiber officinale* into the diet or supplementation with these herbs or magnesium may help to reduce the frequency of migraines by mitigating the possible etiological mechanisms.

There are several theories that have been employed to explain the physiologic processes associated with the onset of migraine HAs. The most prominent are neuronal abnormalities, a platelet disorder, a deficiency of serotonin and mitochondrial dysfunction. All of these mechanisms can initiate an ischemic event.

The neurological dysfunction experienced is due to a defect in the trigeminovascular system, which causes an intense depolarizing wave that suppresses the activity of the brain [4]. Simultaneously substance P is released from the trigeminovascular system [5]. Substance P promotes the release of arachidonic acid (AA), which activates the inflammatory cascade. Inflammation causes the brain to be hypersensitive increasing the probability of an ensuing migraine [6]. Elevated levels of AA are positively correlated with an increased frequency of migraines [7].

Another possible mechanism is associated with abnormalities in serotonin levels. Serotonin levels have a major impact on vascular function. Individuals with a platelet disorder produce irregular platelets that secrete excessive amounts of serotonin [8]. Serotonin acts as a vasoconstrictor predisposing an individual to an ischemic event [9]. On the opposite end of the spectrum, extremely low levels of serotonin generation can increase nociception resulting in hypersensitivity, which can lead to migraines as discussed in the previous paragraph [8].

There has been speculation that impaired mitochondrial function may be responsible for migraine disorders. The theory of mitochondrial dysfunction is centralized around two aspects. One is caused by an alteration of calcium influx into the cell and the second is due to an impaired mitochondrial membrane, which affects mitochondrial permeability [10]. This combination of features predisposes the mitochondria to propagate copious quantities of free radicals that are capable of damaging the mitochondria, other organelles, the nucleus and the cell membrane. Damage to the mitochondria is capable of altering oxidative phosphorylation lowering ATP production [11]. In addition, disruption of mitochondrial function due to free radical damage can potentially induce a mutation in mitochondrial DNA. The DNA of the mitochondria does not possess a repair mechanism [12]. Consequently, alterations in mitochondrial DNA can lead to permanent mitochondrial dysfunction and chronic migraine HAs.

Higher levels of oxidative stress generated from mitochondrial dysfunction increase the probability of neuronal

Introduction

In the United States, migraine headaches (HA) are becoming more prevalent. In 2013, it was estimated that 11.7-16.2% of Americans suffered from migraines according to the American Migraine Prevalence and Prevention study [1]. This number has grown in 2015 and it was projected by the Migraine Research Foundation that 38 million people in the United States suffer from migraine HAs. The Foundation estimates that 25% of households have a migraineur and on a global scale it is the 8th most disabling condition [2].

Background

There are several factors that could contribute to the onset of a migraine HA. The etiological attributes could be from prolonged emotional stress or the exposure to noxious stimuli, which could be visual, auditory or olfactory [3]. The result of the stimuli is an intense vasospasm and subsequent vasoconstriction of the arteries in the head and brain causing ischemia. The ischemic event initiates a reflexive response that induces relaxation of the vasculature resulting in a loss of vascular tone [3]. The atonic blood vessels are fixed in vasodilation and continuously contract in an attempt to reset their elasticity, which induces a pulsating pain. However, due to the intensity of the reflexive response, vasomotor tone cannot be reestablished in some cases for 24-48 hours [3].

damage. Neurons are more susceptible to oxidative injury than other tissues [13]. Impairment can lead to insufficient depolarization that result in hypoxia and subsequent ischemia that can trigger a migraine [10].

There are many different methods of treatment available for individuals that are suffering from migraines. These treatments range from receiving pharmaceutical medications to musculoskeletal care through natural medicine practitioners. However, considering the possible etiologic factors that may be initiating a migraine, it is probable that the addition of functional foods and supplementation could help to relieve and reduce the frequency of migraine HAs.

Discussion

The first theory discussed was the abnormality of the trigeminovascular system that initiates the release of AA and the inflammatory cascade. There is evidence that shows that high levels of AA in circulation is associated with an increased frequency of migraines [14]. The addition of functional foods *Curcuma domestica* or *Zingiber officinale* to the diet may produce a prophylactic effect by inhibiting nuclear factor-kappaB (NF-κB) [11]. NF-κB is the transcription factor that activates enzymes phospholipase A2 and cyclooxygenase [12]. Phospholipase A2 liberates AA, which is the precursor to inflammatory prostaglandins. AA is converted to the prostaglandins by cyclooxygenase [12]. Consequently, inhibiting NF-κB can down-regulate the production of AA and its cascade, which has the potential to prevent or diminish the severity of a migraine. In addition, suppressing the production of AA reduces the levels of leukotrienes. Leukotrienes are generated from AA in a separate pathway that utilizes the enzyme 5-lipoxygenase (LOX) [12]. High levels of leukotrienes are also positively correlated with the development of migraines [15]. Therefore, lowering the levels of leukotrienes can impede the onset or alleviate a migraine.

Other positive attributes that make *C. domestica* and *Z. officinale* particularly suited for the treatment of a migraine are that these herbs act as anticoagulants reducing platelet aggregation [11]. Consequently, reducing the number of platelets in an individual with a platelet disorder can suppress serotonin excretion and the subsequent vasoconstriction that can induce a migraine.

In addition, *C. domestica* enhances the function of the mitochondria, which can help mitigate a migraine due to inadequate mitochondrial function [16]. This could be accomplished by two possible mechanisms. The first is the augmentation of the enzymes in the tricarboxylic acid cycle (TCA) and the electron transport chain (ETC) [16]. Curcumin up-regulates the activity of isocitrate dehydrogenase, which is the rate limiting step of the TCA. Potentiating the effects of isocitrate dehydrogenase has the potential to enhance the production of NADH and FADH₂ in the TCA. NADH and FADH₂ donate electrons to establish the gradient in the electron transport chain (ETC), which is used to generate energy for ATP production [12].

C. domestica has concurrently been shown to potentiate the activity of NADH dehydrogenase (Complex I) and cytochrome c oxidase (Complex IV) in the ETC [16]. Complex I and complex IV are involved with the oxidation-reduction reactions used to create the electrical gradient, which is created from the donation of electrons from NADH and FADH₂. As a result, more energy is available for the production of ATP [16].

The second mechanism is from the antioxidant activity of *C. domestica*. *C. domestica* has been shown to reduce oxidative stress by ten times the amount that vitamin C and resveratrol are capable of [17]. This botanical potentiates the effects of glutathione peroxidase and catalase [17]. In addition, *curcuma* species can enhance the effects of superoxide dismutase (SOD) [18]. Enhancing the physiological effects of these enzymes reduces the production of reactive oxygen species (ROS) and the overall levels of oxidative stress. This prevents ROS from damaging the mitochondria reducing the incidence of DNA mutations and potential impairment of ATP production.

Both of the previous mechanisms discussed can prevent abnormal depolarization of the neurons due to mitochondrial dysfunction. Sufficient depolarizing activity of the neurons reduces the occurrence of hypoxia leading to the ischemic episode that can initiate a migraine. Additionally, *curcuma* species have been shown to enhance cellular viability of neurons preserving their functionality [19].

Although there is not a lot of evidence that demonstrates the efficacy of *Z. officinale* for the enhancement of mitochondrial function, a study done in diabetic rats showed that it increased the mRNA associated with gene expression of the mitochondria [20]. The result of the study was an elevation in mitochondrial components [20]. The effects observed in this study may be due to the ability of *Z. officinale* to act as an antioxidant. Analogous to *C. domestica*, *Z. officinale* can increase SOD, glutathione peroxidase and catalase activity, which reduces oxidative stress and could enhance mitochondrial function preventing abnormal depolarization that could lead to a migraine [21].

Another factor that may influence migraines is that species of *curcuma* and *zingiber* have been shown to interact with transient receptor potential ion channel members (TRPMs) [22,23]. TRPMs conduct nociceptive sensory information and are associated with C fibers, which receive noxious pain information [24]. Mitochondrial dysfunction can activate TRPM [25]. The primary outcome from studies propose that these botanicals may down-regulate nociceptive activity through the activation and consequent desensitization of these receptors [22,23]. Dampening the activity of these receptors may reduce pain perception during a migraine HA. The herbs effect on promoting mitochondrial function may be play a role as well.

Z. officinale has also demonstrated other effects that may reduce the incidence and frequency of a migraine besides anti-inflammatory and anticoagulant activity. This botanical can be used to treat individuals suffering from migraines due to a serotonin deficiency [26]. The ability of *Z. officinale* to interact with serotonin receptors and affect secretion has been

documented [26]. This regulatory activity may alleviate or reduce the occurrence of migraines due to abnormalities of serotonin levels.

A study illustrating the effectiveness of *Z. officinale* for migraines was conducted by Cady et al. In the study, 60 subjects with 221 migraine episodes were treated for 1 month duration. The treatment group consisted of 45 subjects, who suffered from 163 migraine attacks, receiving sublingual extracts of *Tanacetum parthenium/Z. officinale*. The remaining study participants received placebo. In the treatment group, migraines were alleviated in 32% of patients and 63% of patients reported pain relief at 2 hours after administration compared to 16% and 39% of patients in the placebo group [27]. The herbal extract was considered to be significantly effective for the treatment of migraines.

Another consideration for the treatment of migraines would be to supplement with magnesium (Mg). In the US, research has shown that 48% of people have inadequate levels of magnesium in their diet [28]. A diet low in Mg is associated with an increased risk of the development of migraine has [29]. In addition, evidence demonstrates that 50% of migraineurs ingest an insufficient amount of Mg in the diet [30]. Consequently, a relationship between migraine HA incidence and dietary Mg consumption exists.

Mg has been utilized as a prophylactic supplement for migraines [31]. which may be due to its ability to act as a calcium channel regulator [32] Modifying calcium channels promotes vasomotor tone and may help prevent the initial vasospasm associated with an ischemic event preventing a migraine. In addition, defects in calcium channels may be partially responsible for the initiation of migraines associated with mitochondrial dysfunction. As discussed previously, mitochondrial dysfunction could result in higher levels of oxidative stress leading to an inadequate production of ATP and insufficient depolarization. Therefore, regulating the activity of calcium channels may help to prevent impairment of mitochondrial function and alleviate migraines.

Additionally, Mg is capable of potentiating the activity of the mitochondria [33]. This is due to its ability to fortify the mitochondrial membrane increasing the efficiency of the electron transport chain (ETC) [33]. Enhancing the integrity of the mitochondrial membrane and promoting the activity ETC sustains the production of ATP preventing insufficient depolarization in the neurons diminishing migraines [33].

Another consideration is that defects in RPM6 are associated with primary hypomagnesemia [34]. Low levels of Mg are positively correlated with higher levels of oxidative stress and mitochondrial function [35]. Consequently, this may be a possible mechanism that could lead to the development of migraines. In patients with TRPM6 abnormalities, oral supplementation with high dosages of Mg has attenuated magnesium deficiency and is associated with a favorable prognosis [34].

The other effects of Mg that have been observed that are applicable for prophylaxis of migraines stem from its interactions with platelets, serotonin receptors and NF-κB. Mg

may mitigate migraines due to excessive serotonin levels in platelet disorders. In a study conducted by Beltramore et al, supplementing with Mg antagonized serotonin release [36]. Mg has been shown to directly bind to serotonin receptors preventing secretion, which could prevent a migraine from occurring [32]. Furthermore, Mg down-regulates NF-κB preventing the release of AA [37]. Suppressing AA activity hinders the release of pro-inflammatory factors that generate platelets, which can alleviate or reduce the severity of a migraine.

A case report exemplifies the therapeutic effect of magnesium. A 23 year old female had been experiencing migraine HAs for 3 months. Pharmaceutical and musculoskeletal interventions were unable to alleviate her migraines [38]. The signs and symptoms that she presented with were uncharacteristic of common or classic migraines. As a result, she was diagnosed with an atypical migraine [38].

During the history, it was discovered that the patient suffered from a severe case of gastroesophageal reflux disease (GERD). As a result she was prescribed esomeprazole (Nexium), which is a proton pump inhibitor [38]. Proton pump inhibitors are correlated with impairment of Mg absorption [38]. Dietary changes and the supplementation of *ulmus rubra* in conjunction with magnesium and a multivitamin supplementation were administered [38]. The dietary changes and *ulmus rubra* reduced the severity of her GERD, which resulted in decreased usage of esomeprazole. The reduction in the use of esomeprazole in combination with Mg supplementation alleviated the migraines [38]. She has not had a subsequent migraine in two years.

Treatment

C. domestica and *Z. officinale* can be added to the diet within the last two minutes of cooking or taken in capsular forms to produce their positive effects. The addition in the last two minutes of cooking is most appropriate to preserve medicinal value of the botanicals [38]. These botanicals can be prescribed as a supplement as well. The dosage of *C. domestica* ranges from 500 mg to 3000 mg while the dosage of *Z. officinale* is from 200 mg to 1000 mg [11]. These herbs can be used prophylactically or ingested at the onset of a migraine. The dosage of the botanicals would be at the higher end of the spectrum if they are administered at the onset of a migraine. There are side effects and contraindications for both of these herbs, which should be evaluated prior to the incorporation into a treatment plan.

Mg can be administered as a supplement. The appropriate dose for prophylaxis of a migraine is 200-500 mg [32]. Mg can also be consumed in the diet. Spinach contains the highest amount of Mg with 150 mg/cup and seafood has the next highest level with 100 mg per 3 oz. Legumes are considered intermediate sources with 40-50 mg. Absorption of Mg is dependent on the amount of Mg ingested. Lower concentrations in food products have been shown to be well absorbed between 40-60%. Dosages of Mg from 550-850 mg are absorbed between 11-35%. Consequently, intermediate

dosages from 200-500 mg should be absorbed adequately. The botanicals can be used as a monotherapy to reduce the severity or frequency of migraine HAs. Either *C. domestica* or *Z. officinale* or both could be administered in combination with Mg to alleviate or prevent migraines or Mg could be used as a monotherapy.

Conclusion

The incidence of migraines is increasing in the US and worldwide. It is a severe and disabling condition. There are many different etiologic causes attributed to the onset of a migraine. The most common are abnormalities in nerve transmission, a platelet disorder, low levels of serotonin and mitochondrial dysfunction. The incorporation of *C. domestica* and *Z. officinale* into the diet or through supplementation as a monotherapy or in conjunction with Mg can produce prophylactic effects reducing the frequency of migraines.

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