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Migraine management: a review of healthy diets and bioactive compounds

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ABSTRACT:

Migraines are one of the world's leading disabilities, disproportionally affecting women. Socioeconomic challenges worsen the quality of life for migraine sufferers, many of whom express dissatisfaction with current therapies. Since the vascular theory of migraines has already been disproven, current research investigates neurovascular aspects like cortical spreading depression (CSD) and potentially impaired oxygen metabolism in mitochondria. This review aims to assess the efficacy of bioactive compounds such as red wine, CoQ10, caffeine, magnesium (Mg^{2+}), and riboflavin (B_2) in reducing or preventing migraines. A review of current and past literature is used to reach conclusions on these compounds. The goal of researching these compounds is to potentially help decrease cases of excessive medication use or offer complementary options for individuals dissatisfied with their current therapies.

The outcomes of studies regarding red wine are not definitively established, and the ambiguous role of caffeine requires further research on controlled intake and dosage. Compounds such as CoQ10, magnesium, and riboflavin exhibit potential as prophylactic supplements for the reduction of migraine occurrences. Evaluation using the functional food product creation guidelines set by the Functional Food Center has allowed CoQ10, magnesium, and riboflavin to be evaluated up to step 10. Future research should aim to refine the information that remains unresolved from these steps, particularly by addressing factors such as dosage, timing, and frequency of consumption. Additionally, efforts could be directed toward identifying a suitable food vehicle that incorporates all the beneficial bioactive compounds.

Keywords: Migraine; bioactive compounds; functional food; cortical spreading depression; CoQ10; red wine; caffeine; magnesium; IgG-based elimination diet; dietary approaches to stop hypertension (DASH)
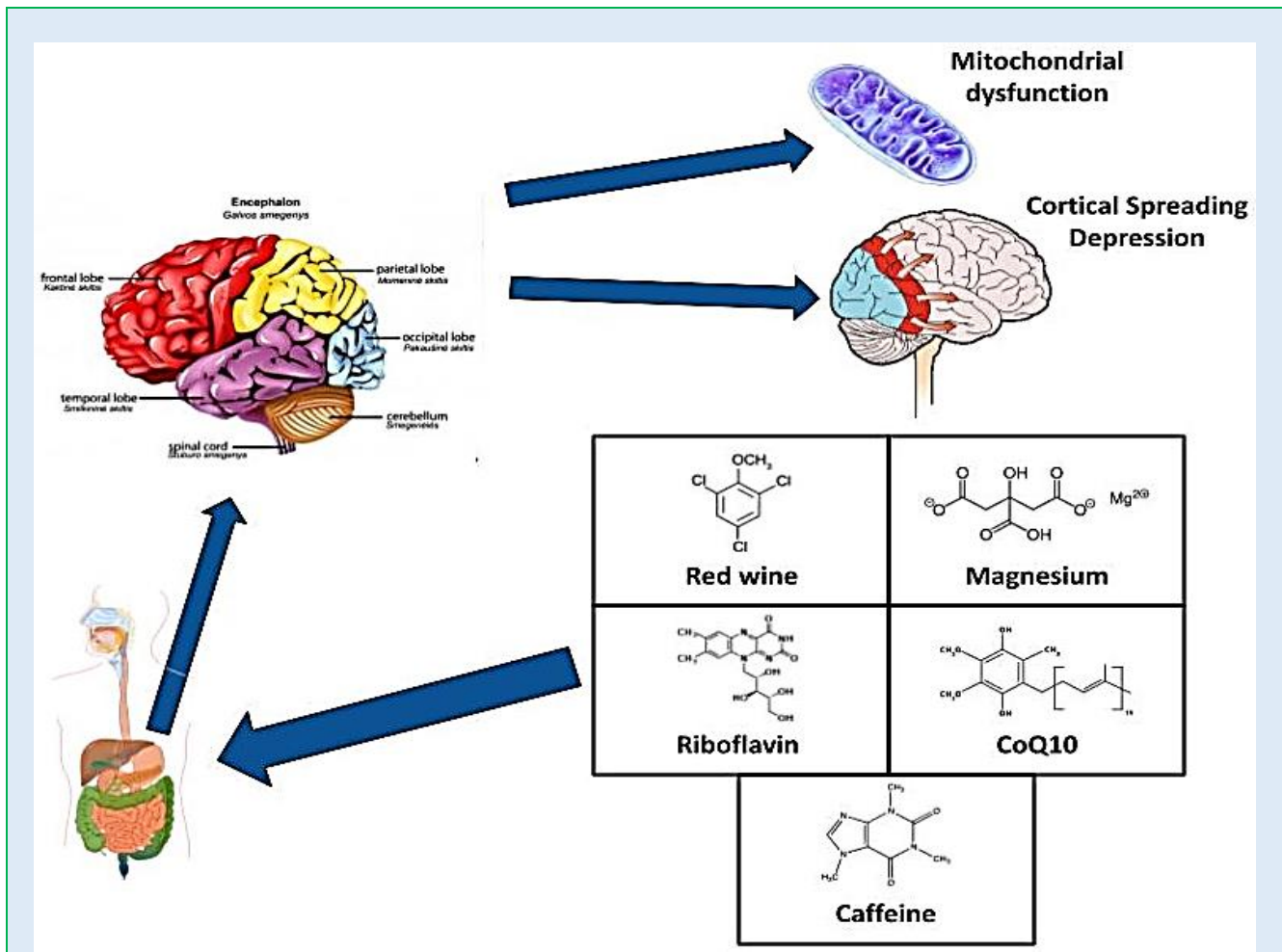
INTRODUCTION

Over 1 billion people worldwide suffer from migraines and medication overuse cases equated to two-thirds of those migraine sufferers [1]. Migraines are the second leading cause of years lived with disability in "high-income, high-middle-income, and middle - [socio-demographic index] quintile countries", following lower back pain [1]. In the U.S., 0.5% of all out-patient visits were primarily to address migraines (4,337,000 people). Between the ages of 15 - 64 years headache and head pain accounted for the third most prevalent reason for why females visited the emergency department. On the other hand, it was the fifth most common for males, according to the 2016 National Hospital Ambulatory Medical Care Survey. Moreover, the National Health Interview Survey stated that 21.0% of females experienced migraines, about double that of males at 10.7% [2]. Despite the fact that more females suffer from migraines, specifically recurrent and chronic, males have an earlier onset [3]. Diagnosis is typically during "early to mid-adolescence" for both males and females, even though it can present at any age, but those with earlier diagnoses tend to be chronic throughout their life [4]. The three main types of migraines can be seen in Table 1. Migraines without aura are moderate to severe headaches that are typically unilateral and/or pulsating and can last four hours to three days and sometimes display symptoms of nausea, photophobia (sensitivity to light), or osmophobia (sensitivity to smell). The minority variant of these migraines, only affecting one-third of total migraineurs, are migraines with

aura and are accompanied by visual or sensory disturbances. A third form, chronic migraines, occurs 15 or more times per month over the course of three months [5]. Migraines negatively affect the quality of life of those who experience them and create socioeconomic burdens. The average cost of migraines per person in the US over the span of three months is estimated to be $1,036 for chronic migraines which is three times greater than the costs of episodic migraines over the same period at $383. In Canada, these costs amount to $471 for chronic migraines and $172 for episodic migraines over the same period [6]. In terms of treatment, prophylaxis entails preventive treatment for recurrent and chronic migraines with common FDA-approved medications: propranolol, timolol, divalproex sodium, and topiramate. Acetaminophen, aspirin, and NSAIDs are suitable for addressing mild migraines, whereas the management of moderate to severe migraines may involve the use of triptans or dihydroergotamine. For some patients, consumption of an initial triptan dose was followed by a more severe migraine within 24 hours which would require a second dose of triptans or pairing with an NSAID for insufficient responses to the triptans [7]. Albeit around 50% of patients felt unsatisfied with their current migraine treatment with 80% considering other conventional therapies or interventions [8].

In 2015, about one-third of adults and 10% of children used complementary and alternative medicines. At this time, it was reported that the complementary and alternative medicine industry's clients were spending between $13.9 to $33.9 billion per year [9]. Theeler et al. revealed that individuals experiencing migraines reported dietary factors at a notably higher frequency compared to patients with other types of headaches [10]. A positive association was found between dietary factors and migraines with aura; this occurred at a higher frequency as compared to migraines without aura. Typical triggers include stress, hormones in women, meal skipping, weather, sleep disturbances, odors, neck pain, lights, alcohol, smoke, heat, food, exercise, and sexual activity [11]. In this review, dietary factors and bioactive compounds are discussed to determine triggers and possibly preventative compounds.

References used in this study were primarily found using the PubMed database by searching terms such as "migraine," "migraine and bioactive compounds," and "migraine and diet," while also referencing internally sourced studies. A total of 103 international sources were used from 1944 to 2023 to compile relevant and reliable data.

Table 1: Classification of three main migraine types

Migraine Diagnosis	Symptoms	Time Span	Frequency
Migraine without aura	In adults: Moderate to severe headache, unilateral and/or pulsating, nausea, vomiting, photophobia, phonophobia, osmophobia. In children: bilateral (rarely pulsating), nausea.	4h to 3 days [5]	

Migraine with aura	Regular migraine symptoms with visual symptoms/loss, sensory symptoms, brainstem symptoms (dizziness, vertigo, tinnitus), speech/language disturbances.	5 - 60 mins [5]	
Chronic migraine	Migraine accompanied by depression/anxiety, medication overuse, low back and neck pain.		≥15 days/month for at least 3 months; on ≥8 days/month, meets diagnostic criteria or responds to migraine medication; loss of periodicity[5]

Possible mechanisms: Some mechanisms have been proposed as to how dietary factors and bioactive ingredients may be linked to the alleviation and even full remedy of migraines. Concrete causation patterns are not proven, yet the consensus is that migraines are the product of inflammation in the body. One pathway of mi-graines in the general sense is through the trigeminovas-cular complex which entails sensory neurons relaying pain signals to the brain [12]. One part of this mechanism, which has now been discredited, was inferred to cause increased blood flow in the brain, more specifically arte-rial and vessel dilation in the cranium such as in the dura, arachnoid, pia, and cerebrum. Magnetic resonance angi-ography tests have proven to be inconsistent with this theory; it is unknown whether the inconsistencies are due to genetic variation, since migraines are genetically related, or if the results simply had no significance [13]. The more accepted concept, the neurovascular hypothe-sis, includes substance P and calcitonin gene–related peptide (CGRP), which are neuropeptides that begin in the ganglion of the trigeminal nerve and travel through non-myelinated and thinly myelinated axons. These neu-ropeptides cause neurologic inflammation and have a no-table role in nociception. Moreover, animal studies have suggested that cortical spreading depression (CSD) may cause neurons and glial cells to depolarize while the ac-tivity in the cortex has ceased [14]. The CSD is accompa-nied by the release of ATP, glutamate, potassium, and hy-drogen ions, which diffuse towards the pia and dura,

their nociceptors are activated, and inflammation occurs [15]. This has only yet been confirmed in animals, but the sequence of reactions is not specified in humans. An-other hypothesized aspect of general migraine experi-ences is mitochondrial dysfunction and inability to properly metabolize oxygen since those who experience migraines have diminished mitochondrial phosphoryla-tion [12].

In relation to the link between diet and migraines, genetic and gastrointestinal origins have been proposed. Since heredity is a large factor in migraine predisposition, epigenetic research shows that abnormal DNA methyla-tion is associated with migraines. For this reason, folate-rich diets have been studied. Although increased folate has been proven to ease migraines, its specific epigenetic functions in the migraine pathways have limited re-search. Nonetheless, there is a greater prevalence of peo-ple with paired gastrointestinal maladies and migraines as opposed to those who experience migraines without gastrointestinal comorbidities [16]. Studies show that re-ductions of gastrointestinal inflammation reduce mi-graine experiences, suggesting an association between migraines and gastrointestinal abnormalities. Using pro-biotics such as selected strains of Lactobacilli and Bifidobacterium could modulate gut microbiota and re-duce inflammation, but further studies are needed to confirm this hypothesis [17].

Habit-Related Triggers: Various migraine triggers have been isolated and studied in relation to dietary intake, especially concerning blood sugar levels and contributors to inflammation.

Irregular eating patterns have a high association with migraines with limited varying evidence. One study by Nazari et al. reported that 37.6% of those who experienced migraines did not eat meals at regularly scheduled intervals as opposed to 17.6% of the control group. Regularly scheduled meals, in this case, did not show a great significance, however, a strong significance was demonstrated when eating less than three meals a day with 29.4% in the migraine group and 9.4% in the non-migraine control group [18]. Another study in San Diego found that the most common factor leading to migraines was skipping meals, as 58.9% out of 112 females reported it to be a precipitating factor [19]. For males, this was less likely the case since only 35.3% claimed that skipping meals lead to experiencing a migraine. Theeler et al. questioned 172 U.S. army soldiers and dependents who attended headache clinics, revealing that fasting was the fourth greatest precipitating factor of migraines with 41% of participants who confirmed this [20]. It is likely, though, that this sample is not representative of the general population since they reported more serious triggers such as military trauma and fatigue. As a supporting view, the *Journal of Clinical Neuroscience* found that nighttime snacking and late dinner meals diminished the chances of migraine experience by 40% as opposed to not eating at all (p = 0.013) [21]. It should be noted that a cross-sectional study of adolescents found no association between migraines and irregular dietary patterns [22]. However, the study was performed with adolescents in the 11th and 12th grades, providing biological variation between this sample and the other studies that included adults. The issue with skipping meals or irregular eating patterns

is the impact on blood glucose levels and homeostatic maintenance. Skipping breakfast, for example, has been proven to cause blood glucose increases after lunch, as one study called it, the "second-meal phenomenon" [23]. It also leads to negative metabolic effects such as insulin insensitivity and increased production of glucose in the liver. From these glucose fluctuations, the CSD period is lengthened by hypoglycemia (about 40 mg/dL) caused by insulin elevation, as found in a mice study [24]. The likely correlation between glucose and insulin homeostasis and migraines is demonstrated with the administration of glucagon, insulin, and leptin decreasing nociception through the trigeminovascular pathway [25]. Furthermore, insulin resistance in the brain is associated with mitochondrial dysfunction, another possible root of migraine episodes, although the chemical mechanism is unclear [26].

DIETARY INTERVENTIONS

IgG-based elimination diet: Since migraines are associated with biological inflammation, foods causing inflammation through sensitivities and intolerances have been studied to relieve migraines. Food intolerances can be tested by the production of Immunoglobulin G (IgG) antibodies, which is related to negative gastrointestinal symptoms and irritable bowel syndrome [27]. A Chinese study analyzed a sample constituted of migraine sufferers and found all participants to have IgG antibodies present while 75.3% had IgG antibodies to specific foods [28]. The IgG-positive group, those with specific food allergens, presented with greater concentrations of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). This is important to consider because IL-6 and TNF-α promote inflammation in the body and sensitize nociceptors; TNF-α leads to increased meningeal nociception while IL-6 decreases the depolarized threshold for dural neurons coming from the trigeminal pathway [29, 30]. A significant

positive association between IgG concentration and results of the Migraine Disability Assessment Questionnaire (MIDAS) indicated a greater impact of migraines on lifestyle, as well as a 1.08 greater likelihood of having chronic migraines in those with higher IgG [28]. Because IgG positive foods have shown strong links to migraines, the elimination diet has been implemented and studied with elimination based on IgG foods. Xie et al. created a study that was the first of its kind, using both the elimination diet and probiotic use. They found that the elimination diet alone and paired with probiotics both decrease MIDAS scores and days of migraine experiences over the course of 7 and 14 weeks [31]. A cross-over study only considering an elimination diet of high IgG-inducing foods established that eliminating these foods decreased the number of times the participants experienced migraines (p = 0.006) and reduced the use of medication (p = 0.006) [32]. Hernandez et al. also reported in their cohort study that an elimination diet for 1 - 6 months of high IgG antibody foods that a statistically significant decrease in migraines was present as well as a complete cessation in 76.79% of subjects (n = 56) [33]. A six-week double-blind crossover clinical study consisting of a sample who were diagnosed with both irritable bowel syndrome (IBS) and migraine used two diet assignments, "provocation" and "elimination" based on individual IgG immunoassay tests of 270 foods [34]. This study found statistically significant benefits in well-being and happiness as well as 66.7% of the patients with at least a 30% reduction in migraine experiences and 47.6% with at least a 50% reduction. These reductions were significant regarding the number of migraines, severity, duration, and use of medication. The one main limitation was that

85.7% of the sample consisted of female patients, but biological sex has already been suggested to influence migraines since a greater frequency of females are affected, especially those of moderate to severe intensity [35].

DASH: The dietary approaches to stop hypertension (DASH) diet has primarily been used for the cause it was created, which is to prevent and ease hypertension. This diet consists of fruits, vegetables, whole grains, and low-fat dairy to decrease the consumption of sodium and potassium [36]. As previously illustrated, migraines are influenced by the homeostasis of blood vessels and are, therefore, influenced by blood pressure mechanics and the role of sodium in this mechanism. The Swedish cohort study by Ibsen from 1997 to 2009 reported a proven association between the DASH diet and reduced risk of heart failure in association with reduced systolic blood pressure [37]. A migraine study of 266 female patients between the ages of 18 and 50 years found a 30% reduction in migraines in those who most consistently followed the diet compared to those who did not strongly follow the diet [38]. A 12-week study conducted a randomized control trial of 102 women between the ages 20 and 50 who were assigned to the control or to the DASH diet specified by a designed menu [39]. The researchers discovered significant decreases in migraine severity (p < 0.01), frequency (p = 0.025), and duration (p = 0.053), as well as fewer depressive symptoms (p = 0.019) in comparison to the control. Duration seemed to be the least affected aspect, but severity, frequency, and depression were both strongly associated with DASH. Overall, the use of the DASH diet and evidence is new and limited to mostly female participants. There is a strong association that has been exemplified through multiple studies proving that DASH is associated with reduced migraines, however, these studies are more recent and males have not

yet been tested in depth with the use of this diet. A prospective study on 40 potential precipitating factors discovered a lack of a relationship between alcohol and migraines even though 60-80% of the patients out of the 325 analyzed drank alcohol for 7-10% of the days logged [40]. From this study, red wine was one of the most frequently consumed drinks in comparison to other types of alcohol. A blind study on a sample of migraine patients compared the effects of red wine (n = 11) vs. vodka (n = 8) with and without dietary controls [41]. About 82% (n = 9/11) of the patients assigned to consume red wine experienced migraine onset, but none of those from the vodka group did.

Red Wine: Red wine is a controversial substance in the field of health since there is scientific disagreement on the aspects of its benefits ranging from preventing heart disease to being a possible trigger of migraines. It contains antioxidants such as catechin, epicatechin, quercetin, anthocyanin, and resveratrol which prevent the synthesis of pro-inflammatory compounds [42]. A phenomenon, labeled the "French paradox," describes a diet of high saturated fats and red wine in observance with lower levels of coronary heart disease as compared to countries [43]. These possible benefits have been attributed to antioxidants such as quercetin and its role in nitric oxide production as well as phenolics [44]. Quercetin's vasodilatory effects may play a role in migraine nociception, but promising anti-inflammatory and neuroprotective effects bring potential to migraine prophylaxis [45]. The 2017 study by Tverdal showed an increase in HDL cholesterol, a higher number of non-alcoholic drinkers who died from cardiovascular disease (CVD) compared to alcoholic drinkers, and a strong negative relationship between wine and CVD [46]. There are still mixed results, especially on the matter of frequency of

consumption. Nevertheless, controversial results about alcohol (without denoting a certain type) and the association with migraine frequency are present, but multiple studies found that red wine was the type of alcohol that had the greatest and most consistent association. One study on Croatian adults utilized surveys to evaluate precipitating factors in 720 migraine patients and 1319 tension-headache patients [47]. They found a significant positive association between red wine and migraines with aura, with a lessened effect on migraines without aura (p < 0.0001). Although, no raw data was presented so it is unknown to what quantitative extent the patients were affected. It is important to highlight that within the sample, 77% (n = 555) of individuals with migraines experienced at least one precipitating factor for their headaches, while 54.9% (n = 725) presented with such factors to a diminished degree (p = 0.003). One outlying study by Aamodt et al. discovered a different relationship since increased alcohol consumption was correlated to a decrease in migraine experiences (p < 0.0001) [48]. Those who drank wine and liquor were 0.8 times less likely to develop migraines as compared to those who were abstinent for two weeks, even though alcohol abusers were 1.5 times more likely to develop a migraine in chronic patients. Even though the patients were abstinent for two weeks, their prior alcohol consumption was not elaborated upon, and the study did not mention possible withdrawal and associated symptoms. The mechanistic causes of why red wine may lead to migraines are not fully understood, however, some pathways have been isolated. Queipo-Ortuño et al. performed a controlled, crossover intervention study where blood, fecal, and urine samples were collected, and molecular assays identified the microbial profiling in each participant [49]. There were different testing periods of different alcohols

consumed as well as a baseline period, but specifically after the red wine period, there was a pronounced elevation in the concentrations of *Firmicutes, Enterococcus, Bacteroides, and Prevotella* bacteria paired with a decrease in *Clostridium* genera and *Clostridium Histolyticum*. Because of these results, the study concluded that red wine has a prebiotic effect on the body, attributed to its polyphenol content. Red wine's regulatory effect is suggested on these bacterial strains, which is especially important when considering the Clostridium strains which have been linked to colon cancer, inflammatory

BIOACTIVE COMPOUNDS

CoQ10: The molecule Coenzyme Q10 (CoQ10), shown in Figure 1, is a hydrophobic phenol found in various plants and is a biological quinone found in aerobic organisms, specifically in the mitochondria [53]. It is typically found in animal products such as oily fish (like salmon or tuna) and organ meats (liver), but it can also be found in whole grains and isolated supplements [54]. Its role is evident in the electron transport chain (ETC) during ATP production in the mitochondrial inner membrane, where it acts as an electron carrier, denoted by its ability to donate, and accept electrons [55]. The benzoquinone ring on the molecule allows it to be a lipophilic antioxidant, protecting against free radicals and oxidation inhibition of lipids, proteins, and DNA, whereas the active form is in its reduced state [56]. The antioxidant properties have already been tested in other circumstances, in which one study proved it to benefit the quality of life in a population of women, considering vitality, emotional, mental, and social aspects [57]. CoQ10 combats endothelial dysfunction, blood vessel lining, by enhancing the release of nitric oxide through stimulation [58]. With a decrease in nitric oxide, endothelin-1 (ET-1) production is not blocked and then becomes uncontrolled, inducing vasoconstriction which contributes to CSD [59]. Mitochondrial

bowel disease, uric acid, serum lipids, and high blood pressure [50]. Considering these results, red wine is not likely to affect the onset of migraines through a gastrointestinal pathway. It is more likely that red wine and other darker-colored alcoholic beverages are associated with migraines due to their content of congeners [51]. These congeners are highly found in red wine and are linked to "hangover" headaches, primarily due to an inflammatory effect as well as intracranial vasodilation which goes back to CSD [52].

dysfunction has been linked to dysfunction of vascular tone control because mitochondria play a role in the homeostatic regulation of intracellular calcium (Ca^{2+}) and -oxides, specifically, reactive chemicals formed by diatomic oxygen [60]. The link between neuronal function and mitochondrial function is that the neuronal cells lose function and possibly die once energy production is depleted through mitochondrial dysfunction. Ca^{2+} is a known initiator and regulator of smooth muscle contraction, not excluding cerebral vessels. It has been proposed that mitochondrial dysfunction can be caused by a deficiency of CoQ10, leading to reduced function in complexes I + III or II + III, CoQ binding sites during respiratory redox reactions [61]. Through in vivo phosphorus magnetic resonance spectroscopy (n = 91), the occipital lobes of the patients with migraines had mitochondrial dysfunction through a reduction in free-energy release during ATP hydrolysis [62]. CoQ10 has been proven to prevent apoptosis by obstructing the opening of mitochondrial pores, which offsets the membrane potential (from $\Delta\Psi$ -180 to 0 mV) needed to complete its task of oxidative phosphorylation driven by proton pumps [63]. The proven clinical aspects were found in a study of 1,550 patients where 32.9% were deficient in CoQ10, indicating a

common deficiency. After supplementation of the deficient sample (1-3 mg/kg/day), migraine frequency diminished by 50% in 46.3% of the sample (p < 0.001) in addition to a significant reduction in MIDAS scores [64]. Dahri et al. found that CoQ10 supplementation at a dose of 400 mg/day for three months reduced levels of CGRP and TNF-α, but not IL-6 and IL-10. These findings suggest a prophylactic effect of CoQ10 supplementation for migraine since it was associated with "less severe, shorter, and less frequent headaches" [65].

A prophylactic study of CoQ10 supplementation in 43 migraine patients (with and without aura) used a double-blind randomized method in two groups, a placebo (control) and the supplementation group which received a 100 mg CoQ10 supplement three times daily [66]. After four months, it was recorded that supplementation provided 50% of the sample with a clinically significant decline in their frequency of migraine attacks compared to the placebo group as well as lessened migraine-associated nausea, specifically during the third month of treatment. Another study only utilized half the dosage of the Sandor et al. study (150 mg per day) and did not use a placebo but utilized the same duration structure of one

baseline month and three treatment months [67]. The results exhibited 61.3% of the sample who had at least a 50% reduction in migraine days and 93.5% with at least 25% benefit (p < 0.0001); a mean decrease of 55% regarding the frequency of attacks also resulted (p < 0.001). An additional investigation using a dosage of 300mg added curcumin supplementation to the methodology in 100 migraine sufferers over the course of eight weeks [68]. This study entailed the division of participants into four groups: a placebo supplement, an 80 mg nano-curcumin supplement, three doses of 100 mg CoQ10 supplements (amounting to 300 mg per day), and one group who received both the nano-curcumin and CoQ10 supplements. From this study, the group supplemented with both nano-curcumin and CoQ10 showed the greatest mean reduction in the frequency of migraine attacks (-3.61), followed by the CoQ10 group (-3.08) then the nano-curcumin group (-1.91). Nonetheless, Slater et al. completed a CoQ10 supplementation study that disputed these findings [69]. Their double-blind crossover study in 50 children revealed that a 100 mg supplement of CoQ10 and the placebo both reduced migraine severity, frequency, and duration at non-comparable rates.
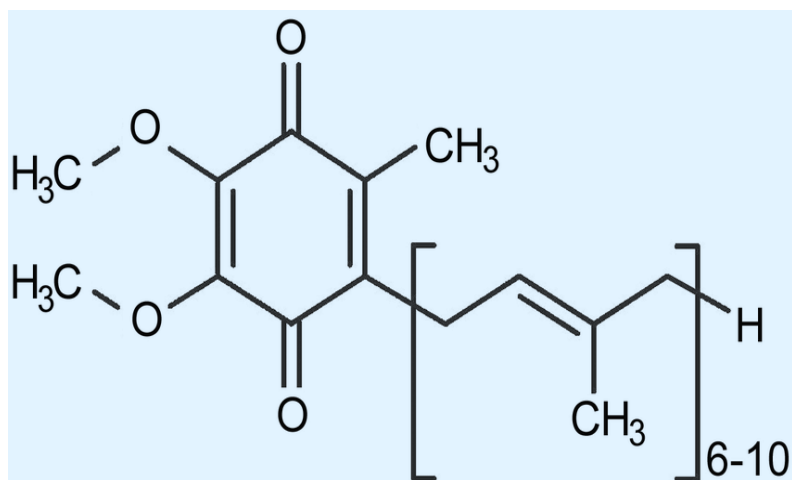

Figure 1: Coenzyme Q10 molecular structure [70]

Caffeine: Caffeine is a commonly used substance worldwide with it being the most commonly used psychoactive drug [71]. It is a biogenic alkaloid (Figure 2), predominantly found in plants such as coffee, tea, soft drinks, and energy drinks [72]. Despite its known abuse and addiction, caffeine is used in many common over-the-counter analgesic drugs such as Excedrin, Midol, Vivarin, Anacin, etc, which are all medications used to combat pain from headaches and migraines [73]. This is due to the fact that caffeine competitively binds to adenosine G-coupled receptors (A1 and A2A) to inhibit them through a mechanism of nonselective antagonism [74]. The A1 receptors are the most prevalent adenosine receptors and are found in the central nervous system (CNS) in areas such as the neocortex, cerebellum, hippocampus, and dorsal horn of the spinal cord [75]. This receptor primarily controls the inhibition of adenylate cyclase, causing an increase in cyclic adenosine monophosphate (cAMP) and the release of mediators that are dependent on IgE antibodies [76]. The A2A receptors are found in the peripheral nervous system and CNS in synaptic terminals on the nerves as well as astrocytes and the blood-brain barrier (BBB) [73]. The agonists are pro-nociceptive which is why the antagonists that attempt to target these receptors are anti-inflammatory medications. The competitive binding by caffeine on these receptors has been linked to an increase in nitric oxide production as well as vasodilation, but caffeine is such an ambiguous substance that it has multiple effects on both of these factors. Adenosine, previously mentioned, is a vasodilator that acts when the A2A receptor stimulates the release of nitric oxide from endothelial cells. Caffeine interferes with this pathway and leads to a diminution of nitric oxide release, causing impairment in the endothelial cells [77]. Caffeine can reach the A2A receptors because it is able to cross the BBB without restriction [78]. Inversely, adenosine uses

the A1 receptor to decrease nitric oxide release and initiate vasoconstriction where caffeine again interjects to inhibit this and increase nitric oxide release to benefit endothelial cell function. The ambiguous effect of caffeine is rooted in variances of dosage, binding affinity to the receptors, and frequency which will determine the action; even though cerebral vascular regulation is not a proven trigger of migraines, it does contribute to pain.

An additional factor contributing to the potential induction of migraines by addictive caffeine use is dehydration. As previously described, caffeine competitively inhibits the A1 adenosine receptor, which leads to a diuretic effect [79]. Dehydration is a known precipitator of migraines, although the underlying mechanisms are still not entirely comprehended. It is proposed that dehydration causes "brain dehydration" through the hypertonic effects experienced by the body, resulting in tension on the "pain-sensitive meninges" and cerebral blood vessels [80].

In a retrospective study involving 50,483 participants, both migraine and non-migraine headaches were linked to caffeine consumption. Those who consumed a high amount of caffeine (>540 mg/day) were 1.1 times more likely to experience headaches [81]. A Japanese study suggested that caffeine might trigger headaches when chronically abused, while also serving as a preventive measure when not overused. Consuming caffeinated coffee/tea daily led to a 2.4 times higher likelihood of developing migraines ($p < 0.0001$), whereas occasional or complete lack of consumption had a minimal effect [82]. In contrast, a study by Rasmussen et al. found no connection between coffee and migraine/tension-type headaches [83]. A further study centered on children and adolescents evaluated caffeine intake using Coca-Cola, given the young participants' high consumption. Their daily consumption totaled 1.5 L, equivalent to 192.88 mg of caffeine per day. Over a span of 2 weeks, a gradual ces-

sation of caffeine led to 91.67% (33 out of 36) experiencing relief from chronic headaches [84]. Another study involving 151 migraine clinic patients highlighted caffeine withdrawal coupled with sleep pattern changes. Results showed that those with weekend migraines had a higher caffeine intake (mean 734 mg caffeine/day) compared to less frequent weekend migraine sufferers (mean 362 mg caffeine/day). Weekend migraines were also associated with 0.8 hours more sleep, with 69% of the participants experiencing migraines with both extra sleep and high caffeine intake [85]. Thus, the issue might not be caffeine itself, but rather a withdrawal from chronic high-caffeine use. Nevertheless, the utilization of a low dose of caffeine (≥65 mg) in combination with pain-relieving medications might amplify drug efficacy by 40%. In a compilation of trials, caffeine withdrawal-inducing migraines occurred in up to 56% of participants. Interestingly, these headaches could be reversed within 30-60 minutes by consuming more caffeine, underscoring the possible caffeine-migraine connection [86].
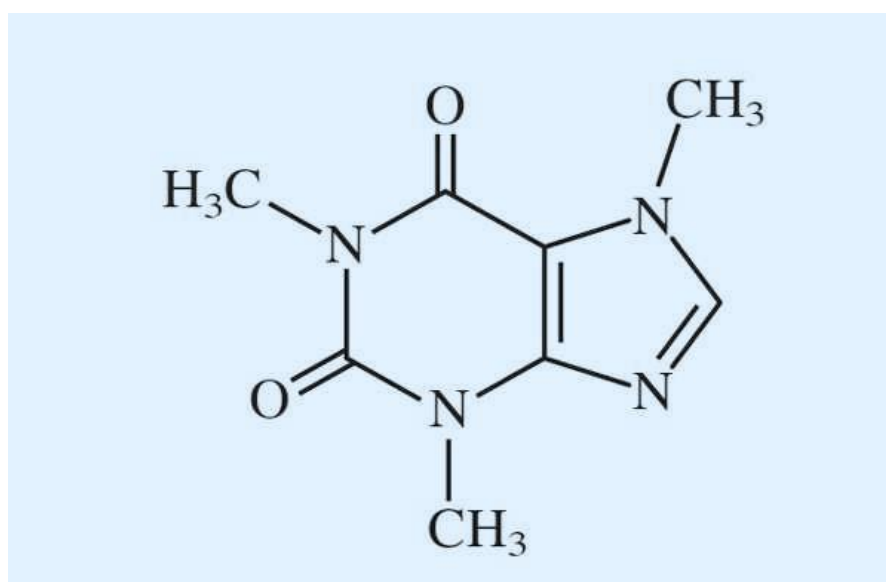

Figure 2: Caffeine molecular structure [87]

Magnesium: Magnesium (Mg^{2+}) is an abundant cation found in the human body that aids many metabolic reactions as a biological cofactor [88]. About 25g of Mg^{2+} can be found in the adult body, but dietary sources include green leafy vegetables (e.g., spinach and kale), legumes, nuts, seeds, whole grains, fortified foods like cereal, and water (tap, mineral, and bottled). It is also taken as an oral or intravenous supplement, typically in the form of magnesium oxide, citrate, and chloride [89]. CSD has already been established as a causative pathway to initiate migraines, but it has many sources of its onset, especially including the N-methyl-D-aspartate (NMDA) receptor [90]. Mg^{2+} blocks NMDA receptors at a resting membrane potential, thus prohibiting excessive activation of this channel, or otherwise identified as excessive firing leading to vasodilation [91]. Magnesium binds to the receptor via voltage dependence as an antagonist of said receptor. Magnesium has been tested for neuroprotection due to the findings that hypomagnesemia is o

served in those presenting with migraine [92]. Results indicate that low levels of magnesium in migraine experiencers are found in serum concentrations, cerebrospinal fluid, ictal and interictal brain regions, and salivary concentrations. One study on oral magnesium loading (3000 mg/24 hrs) in migraine and non-migraine patients exhibited Mg^{2+} retention [93]. This conclusion was reached because serum concentrations of Mg^{2+} in the excreted 24-hour urine were significantly lower in the migraine group, implying a heightened necessity for the preservation of higher levels of Mg^{2+}. Magnesium plays an integral role in neurotransmitter regulation and has been linked to CSD as well as neurogenic inflammation [90]. During CSD, when the BBB's permeability increases, Mg2+ concentrations are lowered and in turn, the NMDA receptors are easily depolarized [94]. Vink et al. identified neurogenic inflammation mediated by substance P which was induced through Mg2+ deficiency in rats [95]. Brain injury triggered a decline in intracellular free Mg^{2+} concentration in the brain to 0.27 ±0.02 mM after a baseline of 0.51 ±0.05 mM. The rats were then treated with substance P antagonist which increased the intracellular free Mg^{2+} concentration to 0.47 ±0.06, not fully restoring the concentration, but proving a higher significance than the control of saline treatment. A clinical study of 12 female patients with Raynaud's Phenomenon, specifically those with the primary form, looked at the administration of intravenous magnesium sulfate and a calcium antagonist to evaluate CGRP levels [96]. Magnesium reportedly decreased CGRP levels in the patients with Raynaud's ($p < 0.05$), but no changes in the healthy subjects. Regardless, Mg^{2+} has been shown in other studies to affect CGRP

levels, indicating its anti-inflammatory role [90]. By decreasing circulating CGRP and substance P, CSD is likely to occur, so migraines with aura are theoretically prevented by regulating adequate magnesium levels.

A placebo-controlled study took place using 20 patients affected by menstrual migraines with a double-blind control group and an experimental group that was assigned to a daily oral magnesium supplement, magnesium pyrrolidone carboxylic acid (MAG), which contained 360 mg of Mg^{2+} [97]. After 2 months, the intensity and duration of migraine attacks decreased in both groups, although the most significant difference was present in the MAG group ($p < 0.03$). Additionally, the MAG group experienced a reduction in the number of days with headache from 4.7 ±3.1 to 2.4 ±2.2 ($p < 0.01$). Peikert et al. conducted a similar investigation over the course of 16 weeks (four-week baseline and 12-week treatment period) in 81 patients between the ages of 18 and 65 who suffer from migraines [98]. With a daily dose of 600 mg, the frequency of headaches lessened significantly in the magnesium group (- 41.6%) compared to the placebo group (- 15.8%) during weeks 9 - 12 ($p < 0.05$). There was also a greater decrease in the number of migraine days in the magnesium group (-52.3%) as opposed to the placebo group (19.5%), yielding a confirmed significance of $p = 0.0344$. The variables with a noteworthy lack of significance included the duration of attacks as well as the intensity, even though the greater minimization was in the magnesium group. Another prospective, placebo-controlled study demonstrated the administration of 20 mmol magnesium daily in 150 migraine patients in central Europe with at least a two-year history [99]. This phase III clinical trial uses the same methodology as the

other two studies, a four-week baseline and 12-week treatment, yet at a much smaller dosage than the other studies (121.5 mg). During the statistical evaluation, both groups had about a 50% reduction in the intensity and duration of their migraine attacks, but the effects of the drug versus the placebo could not be differentiated, leading to the termination of the study from a null result. Mauskop et al. analyzed 40 patients with acute migraines to assess the efficacy of migraine relief from an intravenous magnesium sulfate ($MgSO_4$) of 1 g. To achieve this, low serum magnesium patients (< 0.54 mmol/L) at baseline were compared to high serum magnesium patients (≥ 0.54 mmol/L) over the course of 24 hours after administration. At 15 minutes after the infusion, 87.5% experienced a 50% reduction in the intensity of pain. A proven benefit from the intravenous solution was determined by 24 hours of pain relief, which occurred in 86% of the low serum Mg^{2+} patients and only 16% of those who had adequate/high serum Mg^{2+} levels at baseline. It was determined that patients with low initial serum magnesium levels would benefit from the intravenous solution 27.9 times more than patients with adequate/high serum magnesium levels ($p < 0.0001$) [100].

Riboflavin: Riboflavin, known as vitamin B_2, is a water-soluble vitamin (Figure 3) and cofactor in the body's metabolic pathways such as energy production and cellular function. It usually acts as a precursor for flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) which are the active forms of B_2 [101]. FAD is primarily stored by the liver, while FAD, FMN, and protein-bound riboflavin are released by gastric acid and proteases. The

ATP-dependent hepatocyte riboflavin transporter up-takes riboflavin to phosphorylate it into FMN and then into FAD. The transporter must contain flavokinase, an FAD synthetase, in order for this metabolic reaction to occur. In the mitochondria, FAD and FMN are electron carriers that aid during the oxidation-reduction reactions and the Krebs cycle [102]. B2 can be found mostly in animal products (e.g. eggs, organ meats like kidney and liver, lean meat, and milk), but it is also present in some vegetables and fortified grains and cereals [103, 104]. The recommended daily values for B_2 is 0.4 mg in infants, 0.9 - 1.1 mg in adult men, 1.1 - 1.3 in adult females, and further additions to accommodate pregnancy (+ 0.3 mg) and lactation (+ 0.5 mg). Deficiency has been linked to neurological diseases, specifically migraines, through the role of B_2 in mitochondrial function. It is well-corroborated enough to be considered a Level B treatment for migraines, as established by the American Academy of Neurology [105].

In 1996, a parallel and double-blind study was conducted to compare a high B_2 supplementation (400 mg) and a placebo in 55 adult patients who had at least a one-year history of migraines and who experienced between two and eight migraines per month. A one-month baseline was assessed with a placebo and the treatment proceeded over the course of three months. By month four, there was a significant decrease in the number of headache days ($p = 0.012$), frequency of migraine attacks ($p = 0.005$), and days with nausea experiences ($p = 0.024$), while the placebo group underwent no such changes of significance [106]. Another study focused on the CSD phenomenon, which has been recognized as a migraine

precursor, regarding neuronal activity, specifically, auditory evoked cortical potentials (AEP). This study compared the efficacy of beta-blocker and riboflavin supplementation by first confirming that people who experience migraines have dysfunctional processing of cortical information ($p < 0.001$). Both the beta-blockers and riboflavin supplementation were correlated to a decrease in migraine frequency ($p < 0.05$ for both groups). Riboflavin prescription led to no changes in information processing in the brain ($p = 0.47$) and more likely targeted mitochondrial functions even though the beta-blockers did have a significant correlation with AEP dysfunctional improvement ($p = 0.02$) [107]. A retrospective, pediatric (range: 8 - 18 years), dosage-comparison study evaluated 41 migraine patients who would be divided to take 200 mg/day or 400 mg/day. After six months of treatment, 68.4% of the patients claimed at least a 50% diminishment in the frequency of migraine attacks, along with a 21.0% mitigation in the intensity of those migraines. Despite the significant reduction in frequency and intensity of pediatric migraines ($p < 0.01$), there was no comparison between doses even though the final dosage recommendation was 200 mg/day [108]. Boehnke et al. affirmed the previously mentioned articles through a high dosage of B_2 at 400 mg/day for six months where a significant decrease in migraine frequency ($p < 0.005$) and a 42.9% reduction in attack-relief medication usage ($p = 0.006$) after treatment. It should be noted that duration and intensity had no significant alterations even though the duration variable lessened slightly after treatment [109].
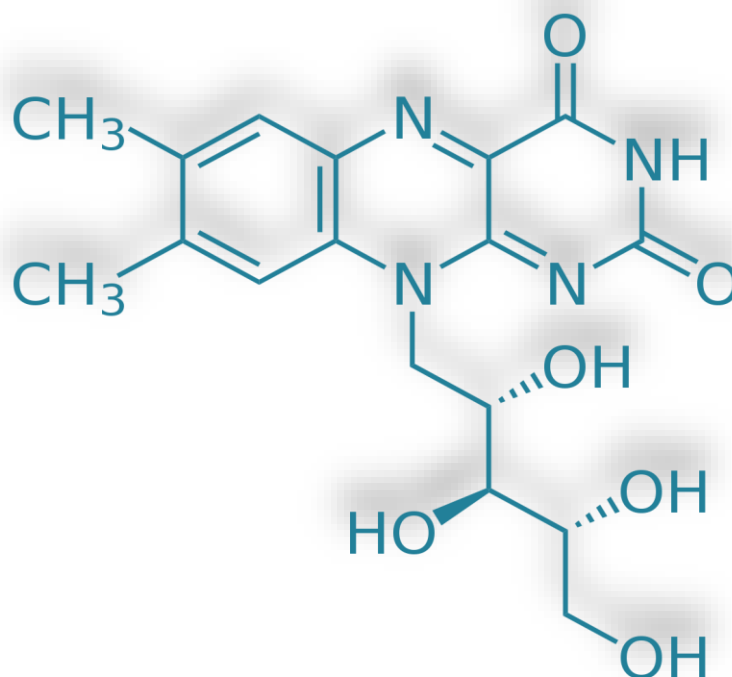

Figure 3: Riboflavin molecular structure [110]

Table 2: Efficacy of various bioactive compounds and nutrients in treating migraines

Bioactive Food/Compound	Study Design, N	Findings	Reference
Red Wine	Literature review, N = n/a	Mediterranean and French diets are associated with health benefits (lower coronary heart disease), but direct causation and pinpointing polyphenols cannot be concluded.	[43]
	In-vitro experimental study, N = n/a	Protein disulfide isomerase is hindered by red wine, but not white wine.	[44]
	Observational cohort study, N = 115,592	Cardiovascular disease mortality is less common in alcohol drinkers (specifically wine) than abstainers.	[46]
	Population-based survey, N = 3,794	Stress, frequent traveling, food triggers (red wine), and weather changes showed a positive relationship with migraines.	[47]
	Population-based cross-sectional study, N = 51,383	Smoking was positively associated with migraines and alcohol use was inversely related.	[48]
	Randomized, crossover, controlled intervention study, N = 10	Red wine polyphenols prevent growth of harmful gut microbiota and benefit growth of probiotic bacteria.	[49]
	N/A	Red wine dark colored alcoholic beverages contain congeners which are associated with migraines.	[51]
	Cross-sectional study, N = 692	Migraine experiencers consume less alcohol (especially beer and liquor) and are more prone to migraine-like hangover symptoms.	[52]
Coenzyme Q10	Clinical study, N = 1,550	CoQ10 deficiency is common in children and adolescent migraine patients, but CoQ10 supplementation (1-3 mg/kg/day) leads to symptom improvements.	[64]
	Randomized double-blind placebo-controlled clinical trial, N = 45	CoQ10 supplementation (400 mg/day) decreased CGRP, TNF-α, and migraine frequency, severity and duration.	[65]
	Double-blind, randomized, placebo-controlled trial, N = 43	CoQ10 (100 mg/3x/day) decreased migraine frequency and reduced associated nausea.	[66]
	Open-label clinical trial, N = 31	CoQ10 supplementation (150 mg/day) reduced migraine attack frequency.	[67]
	Randomized, placebo-controlled, double-blind trial, N = 91	Nano-curcumin (80 mg/day) and CoQ10 (300 mg/day) supplementation decreased frequency, severity, duration of migraine attacks while easing headache diary results.	[68]

Bioactive Food/Compound	Study Design, N	Findings	Reference
	Crossover, double-blind, placebo-controlled, randomized, add-on study, N = 120	Initial benefit of CoQ10 treatment (100 mg) but finally no difference between CoQ10 and placebo.	[69]
Caffeine	Retrospective cross-sectional study, N = 51,383	High-caffeine consumers (>540 mg/day) experienced less frequent headaches than low-caffeine consumers (0–240 mg/day).	[81]
	Population-Based Door-to-Door Survey, N = 5758)	Migraine experiencers ingest significantly more fatty/oily foods, coffee, and tea than those in the same community with no migraines.	[82]
	Cross-sectional epidemiological study, N = 975	No association of smoking, coffee and alcohol consumption with migraine/tension-type headaches.	[83]
	Longitudinal intervention study, N = 36	High-caffeine consumption leads to caffeine-induced headaches, but gradual withdrawal ceases headaches without withdrawal headaches.	[84]
	Retrospective study, N = 151	Chronic high caffeine usage (734 mg/day) (caffeine withdrawal) and delayed awakening on weekends leads to weekend headaches.	[85]
	Narrative review	Chronic caffeine increases migraine prophylaxis, but low-dose acute caffeine usage (≥ 65 mg) prevents prophylaxis.	[86]
Magnesium	Double-blind, placebo-controlled study, N = 20	Intracellular magnesium content is restored parallel to perimenstrual migraine improvement upon oral magnesium pyrrolidone carboxylic acid supplementation (MAG) (360 mg/day).	[97]
	Prospective, placebo-controlled, double-blind randomized Study, N = 81	Migraine attack frequency decreased with oral trimagnesium dicitrate supplementation (600 mg/day).	[98]
	Prospective, randomized, double-blind, placebo-controlled study, N = 69	After 16 weeks of 20 mmol oral administration of magnesium-u-aspartate-hydrochloride-trihydrate (MAH), lack of differentiation between MAH and placebo led to study termination.	[99]
	Pilot study, N = 40	Patients with serum Mg levels below 0.54 mmol/l are likely to respond to intravenous MgSO4 to relieve migraines for at least 24h.	[100]
Riboflavin	Double-blind, randomized, two-parallel group trial, N = 55	Attack frequency and headache days were reduced with riboflavin supplementation (400 mg/day).	[106]

Bioactive Food/Compound	Study Design, N	Findings	Reference
	Prospective clinical study, N = 26	Beta-blockers (210 mg/day) and riboflavin (400 mg/day) aid migraine prophylaxis, but only beta-blockers ease dysfunctional cortical information processing.	[107]
	Retrospective study, N = 41	Riboflavin supplementation (both 200 and 400 mg/day) reduced migraine attack frequency and intensity.	[108]
	Open-label study, N = 23	Headache frequency followed riboflavin treatment (400 mg/day) with no effect on duration and intensity.	[109]

EVALUATION OF BIOACTIVE COMPOUNDS IN MIGRAINE MECHANISMS: FUNCTIONAL FOOD PRODUCT CREATION AND EVALUATION USING FFC'S GUIDELINES

For these bioactive compounds or nutrients to be considered functional ingredients and to be marketed as such, Figure 4 outlines the 17-step procedure for developing food products for the consumer market, as created by the functional food center [111]. Steps 1 and 2 are explained through this review as aiming to ease and prevent migraines with CoQ10, caffeine, magnesium, and riboflavin. Steps 3 and 4 require further research to establish precise dosage and consumption times, particularly for CoQ10 and magnesium due to wide experimental ranges. Daily consumption is advised, with possible division of the CoQ10 dosage throughout the day based on future findings. Table 2 suggests a typical consumption of 400 mg of riboflavin per day in a single dosage, and caffeine consumption at around ≥65 mg. However, the upper limit for caffeine remains uncertain with this article proposing a lower dose of approximately 300 mg for acute management of migraine symptoms (between 240 and 360) upon early onset. Figure 4 addresses the mechanisms of action for step 5 such as the mitochondrial electron transport chain for CoQ10 and riboflavin, adenosine receptors using competitive caffeine, and CSD-related neurotransmission for magnesium. In step 6, biomarkers were rarely used for caffeine, CoQ10, and riboflavin in examined studies (refer to Table 2), while magnesium's levels can be assessed via serum and intracellular concentrations. Typically, the effects were concluded through MIDAS, diary entries, or other descriptors to indicate the occurrence of migraines. Suitable consumption forms for step 7 include oral supplements for riboflavin and CoQ10, oral magnesium supplements or intravenous MgSO4, and caffeine through pain medications or coffee/tea. Still, more research is needed on determining specific dietary vehicles and the discovery of an item that contains all these compounds would be beneficial.

Step 8 addresses the efficacy and safety of these compounds; no reported side effects for CoQ10, withdrawal from addictive chronic use of caffeine, occasional diarrhea from magnesium, and rare diarrhea and polyuria upon riboflavin consumption. Step 9 still requires further studies to be completed since the previous steps are still incomplete. Step 10 is already underway since isolated

supplements exist for all of the reviewed bioactive compounds excluding caffeine, which exists within pain medications. Although, labels should better highlight the functional properties. For step 11, studies are already

published (Table 2), yet more refined research on dosages and frequencies is beneficial. For step 12, public education should focus on functional food benefits rather than deficiency-centered advertisements.
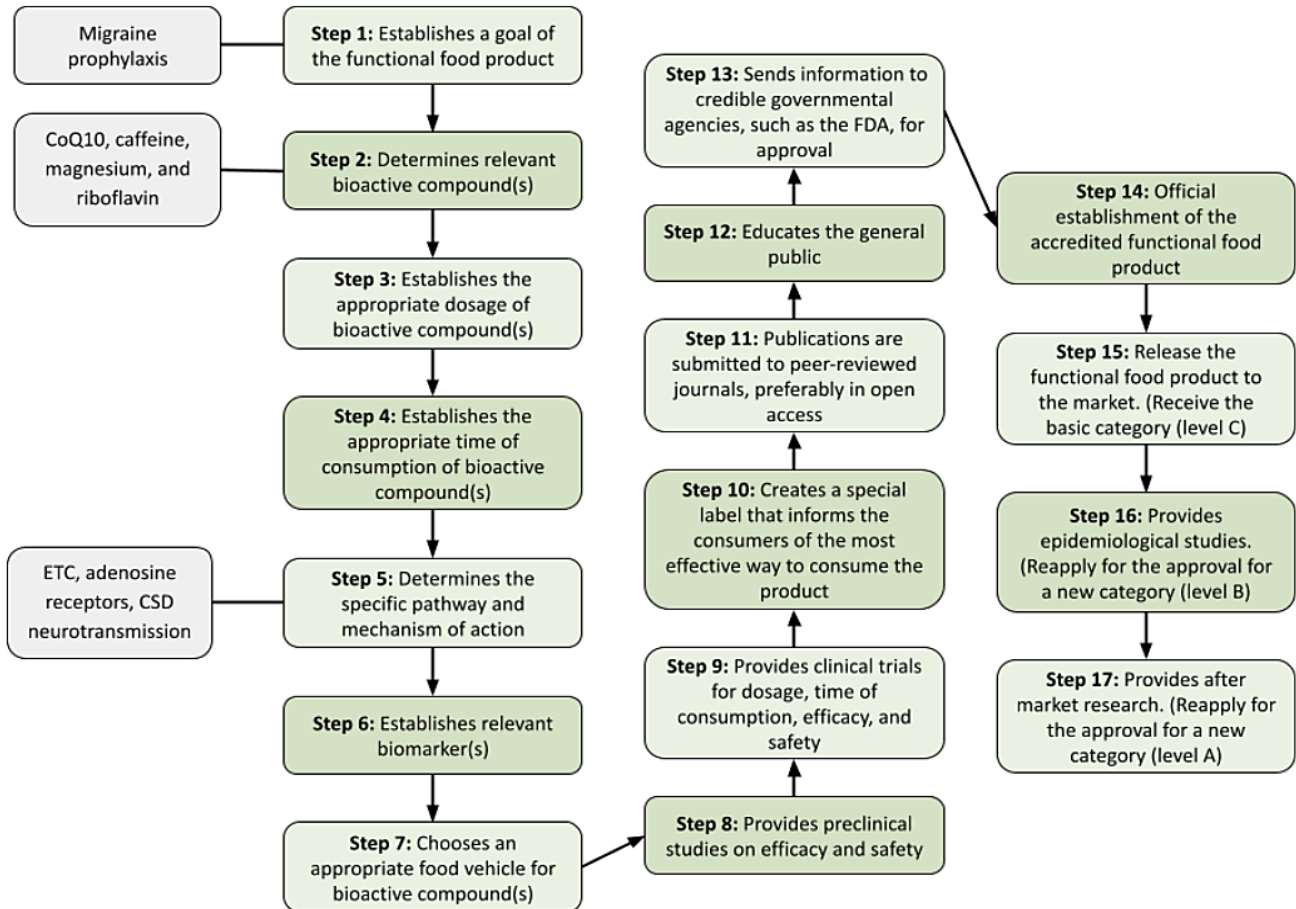

Figure 4: Steps to develop Functional Food Products for market launching as proposed by the Functional Food Center. [111]

CONCLUSION

With high rates of migraines in the international population as well as concerns about medication overuse, bioactive compounds, and nutrients are being increasingly studied as prophylactic methods. Blood glucose control is an initial step in prevention to prevent glucose fluctuations leading to CSD, in addition to IgG elimination diets to reduce the activation of inflammatory neurons.   The DASH diet, once considering its individual bioactive compounds, is not a conclusively beneficial diet on which to base prophylactic treatment because direct mechanisms

cannot be drawn despite some correlations to easing migraine symptoms. Red wine as a specific beverage, with its many bioactive compounds, is inconclusive in the data presented, but it appears that "hangover" headaches should be further investigated as inflammatory responses have been found in relation to CSD. Caffeine is proposed as an effective acute migraine treatment due to its competitive action at adenosine receptors. However, high doses and caffeine addiction or dependence can increase the risk of migraine development, especially in the case of withdrawal. Compounds such as CoQ10,

magnesium, and B₂ have been suggested as effective preventative measures when supplemented in migraine patients, easing frequency, duration, and intensity of the migraines; frequency was the most affected variable. These conclusions were often measured through diaries, rating scales, and the MIDAS assessment. The efficacy of these compounds was particularly attributable to supporting or easing mechanisms related to CSD, mitochondrial function, and the neurovascular theory.

The implications of this study include the implementation of suggested lifestyle changes in migraine patients to prevent or ease migraines without medication overuse since much of the population is already shifting to CAM and looking for alternative treatments to their current ineffective methods. Further bioactive compounds should be studied as well as interactions between these compounds.

The Novelty of This Work: This study reviewed the potential preventive and alleviating impacts of CoQ10, caffeine, magnesium, and riboflavin on migraines and migraine onset. Despite some of these compounds already being in use, they are not considered specific functional food ingredients for migraines, and their uses are not widely recognized by the public. This study suggested the possibility that these compounds could be labeled as functional compounds. However, further research is required to fulfill the 17-step development procedure.

Steps 3, 4, and 7 need to be further defined to increase precision. Steps 8 and 9 should be completed after the previous steps are more accurate. Until steps 1 - 9 are fully complete without the current gaps, steps 10 through 17 can potentially be executed in the future to align with the concept of functional foods, rather than only the isolated bioactive compounds at hand.

Abbreviations: CGRP: calcitonin gene–related peptide, CSD: cortical spreading depression, IgG: Immunoglobulin G, IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, MIDAS: Migraine Disability Assessment Questionnaire, DASH: Dietary Approaches to Stop Hypertension, CoQ10: Coenzyme Q10, ETC: electron transport chain, Ca^{2+}: intracellular calcium, CNS: central nervous system, BBB: blood-brain barrier, Mg^{2+}: Magnesium, FMN: flavin mononucleotide, FAD: flavin adenine dinucleotide, FFS: Functional Food Science Journal

Author's contributions: DM conceived the idea of analyzing the implication of bioactive compounds for the management of Migraine management and discussed it with IS. IS conducted research data gathering and organized information into tables. IS worked on writing the manuscript. DM advised and participated in reviewing articles and editing the manuscript.

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