



Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network



RESEARCH ARTICLE

BIOSCIENCE RESEARCH, 2021 18(2): 1405-1415.

OPEN ACCESS

Clinical effectiveness of apple-quince syrup in chronic migraine: a double-blind randomized controlled trial

Fakhri Allahyari¹, Javad Hosseini Nejad^{1*}, Mina Movahhed², Ahmad Karimi³ and Hamideh Molaee⁴

¹Neuroscience Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

²Traditional Medicine and Materia Medica Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

³School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁴Trauma Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

⁵Exercise Physiology Research Center, Lifestyle Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

*Correspondence: javadhoseini1360@gmail.com Received 09-01-2021, Revised: 12-04-2021, Accepted: 26-04-2021 e-Published: 01-05-2021

Chronic migraine is a disabling and invasive neurological disorder associated with severe episodic and recurrent headaches. To assess the effectiveness of apple-quince syrup on the frequency, severity and duration of migraine headaches. This study was a prospective, randomized, double-blind, parallel-group, controlled, trial between January 2015 and March 2016. Patients who had at least 2 migraine attacks within 4 weeks were randomly assigned apple-quince syrup (n=31), or placebo (n=31). Patients were asked to take the syrup (apple-quince or placebo) 10 ml TFD for 3 months after each meal (three times a day) in a size equal to 10 grams for 3 months.. The frequency (per week), mean duration (hour) and mean intensity (ten-point visual analog scale (VAS)) of headache attacks evaluated at baseline and following 4 and 12 weeks of the intervention. VAS scores were significantly lower in patients treated with the apple-quince syrup compared with patients treated with placebo (Mean Difference:-2.57, 95%CI:-3.49 to -1.66, P<0.001). Apple-quince syrup significantly made higher reduction compared to placebo after 3 months of intervention (Mean Difference:-44.06, 95%CI:-66.80 to -21.32, P<0.001). The number of migraine headache attacks per week in apple-quince group was significantly lower compared to controls after 3 months of intervention (Mean Difference:-3.00, 95%CI:-4.20 to -1.79, P<0.001). Apple-quince syrup is a safe and effective intervention as a first-line abortive treatment for a population migraine that frequently experience mild headache prior to the onset of moderate to severe headache.

Keywords: Migraine, Medicine, Traditional

INTRODUCTION

The headache is the seventh cause of referral to the physician. It occurs in all age groups(Burch, et al 2015). Headache lifetime risk is 95% for women and 90% for men. Migraine is one of the most common headaches. The prevalence of migraine are 18.2% in women and 6.6% in men aged 12 to 80 years(Buse, et al 2013). It occurs in

the second decade of life at first and 90% of patients experience the first migraine attack by the age of 40 years(Smitherman et al. 2013). Typically, every migraine attack lasts about 4 to 7 hours and its severity is such that it affects occupational and individual functions(Diener and Dodick, 2016).

The American Pain Society considers migraine is the fifth most important vital sign and controlling or relieving its pain by pharmaceutical and non-pharmaceutical methods is one of the important challenges in the therapeutic procedure (Marmura et al. 2015). Preventive treatments include beta-blockers, anti-depressants and anticonvulsants. The available evidence shows the response to these treatments has been low and the pain reduction is observed in about 50% of patients so only two-thirds of patients undergoing their drug therapy (Orr et al. 2016). Due to incomplete effectiveness and the adverse side effects of taking medications, the use of non-medical methods for relieving pain has been considered in new studies (Nahin et al. 2016). Non-medical approaches in terms of alternative or complementary therapies, including herbal therapy, temperament correction, therapeutic touch, hypnotherapy, homeopathy, aromatherapy, acupuncture, cupping, etc. (Clarke et al. 2015). Herbal therapy is the most popular complementary therapeutic approach which is more accepted and it has been used to treat migraine in previous studies, (Holland and Ashman, 2012).

Previously, in Iranian traditional medicine (ITM), herbal medicine has been frequently used to treat patients with migraine headaches (Gorji, 2003). One of the basic concepts in ITM is nature or body balances in order to preserve or restore the health of the body. It is a priority to treat the disease and can be achieved by strengthening the body (Mahdizadeh et al. 2015). According to traditional Iranian medicine principles, scented and fragrant medicines are considered strengthening the psyche and organ, and also lead to the survival of life. This principle is used in the treatment of brain and nervous system disorders, including headache. Iranian physicians have also recommended the use of aromatic herbs to strengthen the brain and treat headaches (Zargarani et al. 2016).

Cydonia oblonga M. is a medicinal plant of family Rosaceae which is used to prevent or treat several ailments, such as cancer, diabetes, hepatitis, ulcer, respiratory and urinary infections, etc (Sajid et al. 2015). *Cydonia oblonga* is commonly known as quince and rich in useful secondary metabolites, such as phenolics, steroids, flavonoids, terpenoids, tannins, sugars, organic acids and glycosides (Ashraf et al. 2016). A wide range of pharmacological activities like antioxidant, antibacterial, antifungal, anti-inflammatory, hepatoprotective, cardiovascular,

antidepressant, antidiarrheal, hypolipidemic, diuretic and hypoglycemic have been ascribed to various parts of *C. oblonga* (Al-Snafi, 2016). Apple fruit with a scientific name of *Malus domestica* has been also recognized strengthening brain and effective in the treatment of headaches in ancient Iranian sources of medicine (Gorji, 2003). The aim of this study was to investigate the effect of syrup of apple and quince syrup in improving the frequency, severity and duration of migraine headaches.

MATERIALS AND METHODS

The prospective, randomized, controlled trial study was conducted in Shahid Beheshti University of Medical Sciences, Tehran, Iran, between January 2015 and March 2016 in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines (Turner et al. 2012). The eligible patients with a clinical diagnosis of migraine headache without aura were selected according to 2nd Edition of the International Headache Classification (ICHD-2) (Mentz et al. 2016). The participants were selected according to the defined inclusion criteria, including a history of migraine at least 1 year before study entry, at least 2 migraine attacks within 4 weeks, aged 18 to 60 years old, no current prophylactic treatment for migraine in the past 3 months, no drug abuse in the past 6 months, pain refractory to preventive medications and no underlying diseases. Exclusion criteria included patients with secondary forms of headache, alternative treatment to migraine pain (e.g. acupuncture, massage, biofeedback), a history of significant medical problems (diabetes mellitus and chronic inflammatory disease), drug abuse, abdominal surgery, pregnancy or planning for a pregnancy during the study period, any medical condition that, in the opinion of the investigator, could confound the results of the study. The study was conducted in accordance with the principles outlined in the Good Clinical Practice (GCP) (Malik et al. 2015). The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences Clinical Research Ethics Board, and written informed consent was obtained from each patient before any study-related tests do. The study was registered in Iranian Registry of clinical Trial (www.IRCT.ir) by the number of IRCT2016071929002N1.

After written informed consent was obtained, patients were randomized to two equal groups by

sealed envelope assignment. A randomization plan was developed using an online randomization generator (www.sealedenvelope.com). Permuted-block treatment allocation (ratio 1:1) was used to assign participants to each group. The size of blocks was six. Allocation concealment was maintained by sequentially numbered opaque sealed envelopes until the patient was screened and approved for inclusion. An external operator, who was not involved in the selection and allocation of patients, prepared, coded, and sealed opaque envelopes. The staffs involved in study were blinded to the allocation of patients. Moreover, due to the same shape and size of apple-quince syrup and placebo syrup containers and similarity in syrups appearance, the patients were also blinded to the drug allocations.

Intervention

Making apple-quince syrup

The drug was developed at the Center for Traditional Medicine and Medical Mentors Materia Medika Research center. Apples and quinces required were bought from market. The fruits were washed and disinfected with D7 nanosile infectious agent. Cores and corrupted parts were separated. Their extract juice was taken. Equally extracts juices of apples and quinces were mixed together and passed through the filter. It was boiled in gentle heat to reach the syrup consistency (Equivalent to one seventh volume). Methyl Paraben 0.08% and Propyl Paraben 0.02% were dissolved in hot water and added to the product. Then, the syrup was packaged in matte glasses. The amount of total phenolic compounds in the syrup was measured. Microbial control tests were performed on the product.

Making placebo syrup

Placebo syrup was also produced using glycerin 10%, caramel color in 1 milligram per milliliter and Methyl Parapen% 0.08 and Propyl Paraben 0.02% at the Center for Traditional Medicine and Medical Mutations of Shahid Beheshti University of Medical Sciences. The placebo was packed in 250 ml matt glasses. Microbial quality control tests were performed on placebo. Microbiological control tests were performed on apple-quince syrup and placebo syrup according to the World Health Organization (WHO) method.

Outcome measures

Initially, the basic characteristics and demographic information were registered for two groups. In addition, the baseline frequency, duration and severity of migraine were recorded and patients were asked to express the frequency of migraine attacks and mean duration of pain per a week. Then, the mean severity of pain was evaluated by a ten-point VAS after one month and after 3 months of intervention starting. Patients receive their treatments and at the end of each week, patients were referring to the neurology clinic to report the requested items.

Sample size calculation

VAS score was considered as a primary outcome for sample size calculation. The study required the enrollment of 31 patients in each group to have at least 80% power to detect mean difference of 1.5 between two groups regard to main outcome (with two-sided test and type 1 error of 5%).

Statistical method

For describing the data, the number and percentage were reported for qualitative variables. In addition, quantitative variables were described using the mean (and SD). Comparability among the 2 treatment groups was employed using Student's t-test and chi-squares test. VAS scores 1 and 3 months after intervention were considered as main outcome and the effects of treatment groups, time of recording and interaction of treatments*times were evaluated using repeated measures ANOVA. All analyses were done on the intention-to-treat. All statistical analysis were done using STATA package, version 13 and p-value of < 0.05 was considered statistically significant.

RESULTS

Between Nov 2015 and March 2016, 114 subjects were considered eligible for the study. After the application of exclusion criteria, 62 patients entered the study and were randomly divided into two groups (n = 31 in each arm): apple-quince and placebo groups (Fig. 1). No subjects were excluded from the analysis; no dropout and missing data were recorded. At baseline assessment, the two groups were similar (Table 1).

Effect of apple-quince syrup on migraine headache intensity

The differences in the VAS scores among the 2 groups at each time point are shown in Figure 2.

The mean VAS scores have significantly decreased in the apple-quince group from $6.52 \pm (3.74)$ at baseline to $4.62 \pm (3.13)$ at month 1 and $3.48 \pm (2.52)$ at month 3, whereas in the placebo group from $6.13 \pm (2.42)$ at baseline to $5.72 \pm (2.35)$ at month 1 and $5.67 \pm (2.28)$ at month 3 ($P < 0.001$).

After 3 months, VAS scores were significantly lower in patients treated with the apple-quince syrup compared with women treated with placebo (Mean Difference: -2.57 , 95%CI: -3.49 to -1.66 , $P < 0.001$) (Figure 1).

Effect of apple-quince syrup on duration of migraine headache attacks

In regard to mean reduction duration of migraine headache attacks, apple-quince syrup

significantly made higher reduction compared to placebo after 3 months of intervention (Mean Difference: -44.06 , 95%CI: -66.80 to -21.32 , $P < 0.001$) (Figure 3).

Effect of apple-quince syrup on frequency of migraine headache attacks

Comparing frequency of migraine headache attacks in two groups showed that the number of migraine headache attacks per week in apple-quince group was significantly lower compared to controls after 3 months of intervention (Mean Difference: -3.00 , 95%CI: -4.20 to -1.79 , $P < 0.001$) (Figure 4).

Table 1: Comparison of baseline characteristics of subjects in treatment groups

Characteristics	Apple-quince syrup (n=31)	Placebo (n=31)	P-value
Age	$40.77 \pm (10.37)$	$41.96 \pm (9.80)$	0.643
BMI	$26.44 \pm (5.22)$	$25.74 \pm (3.44)$	0.539
Gender			
Male	11 (35.5)	16 (51.6)	0.200
Female	20 (64.5)	15 (48.4)	
Duration of migraine (mean \pm SD)	$80.93 (79.79)$	$61.35 (27.82)$	0.205
Visual Analogue Scale (VAS)	$6.52 \pm (3.74)$	$6.13 \pm (2.42)$	0.631
Frequency of migraine	$10.25 \pm (5.84)$	$9.19 \pm (3.51)$	0.389

Values given as mean \pm SD (standard deviation), or number (percentage) unless otherwise indicated

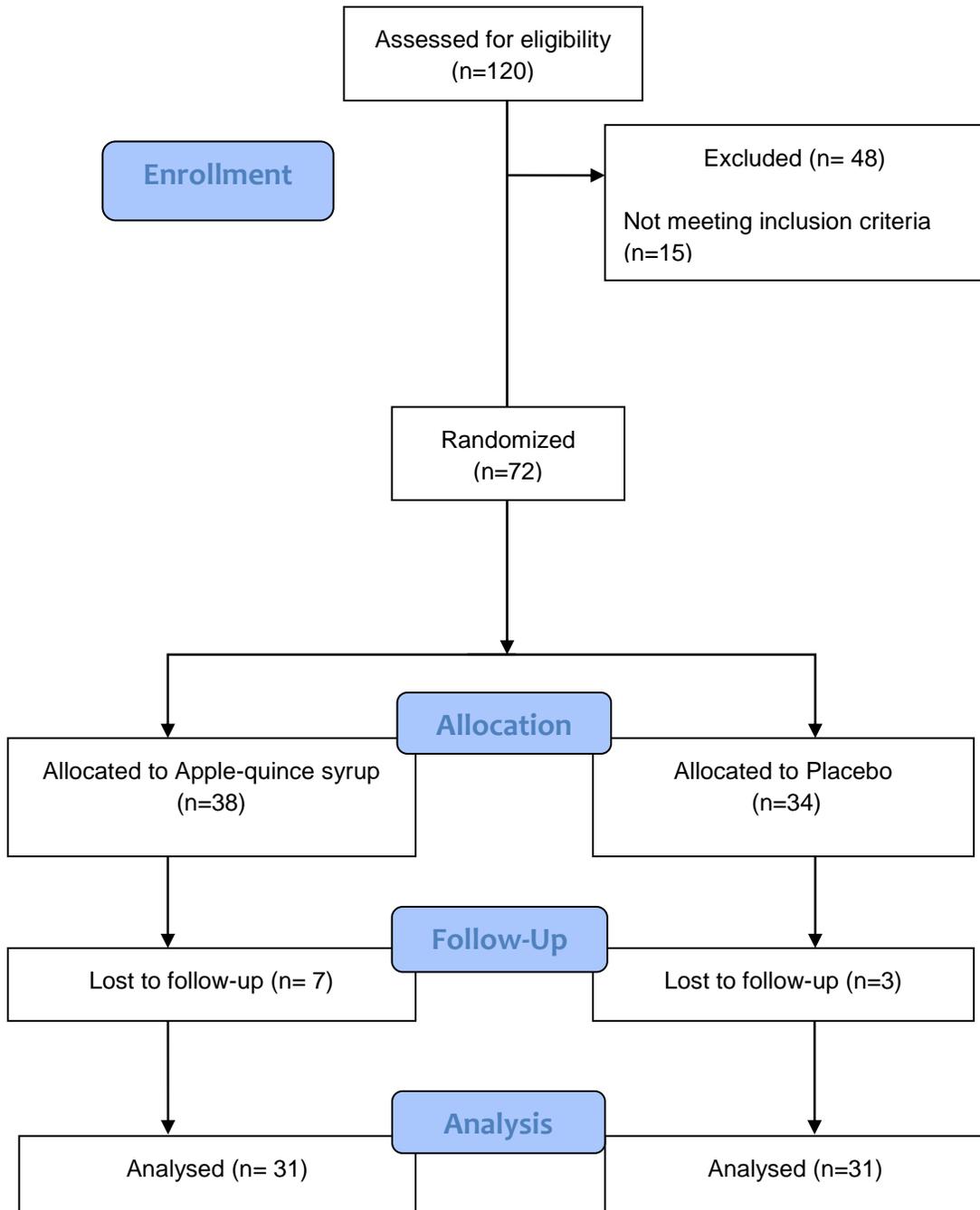


Figure1: The flowchart of study inclusion, allocation and follow-up.

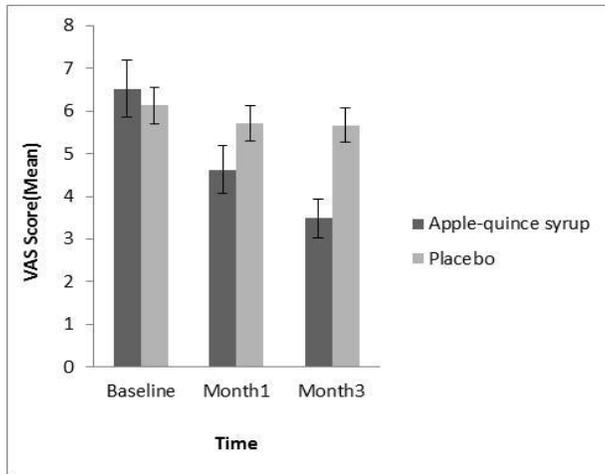


Figure 2: VAS scores at various time points

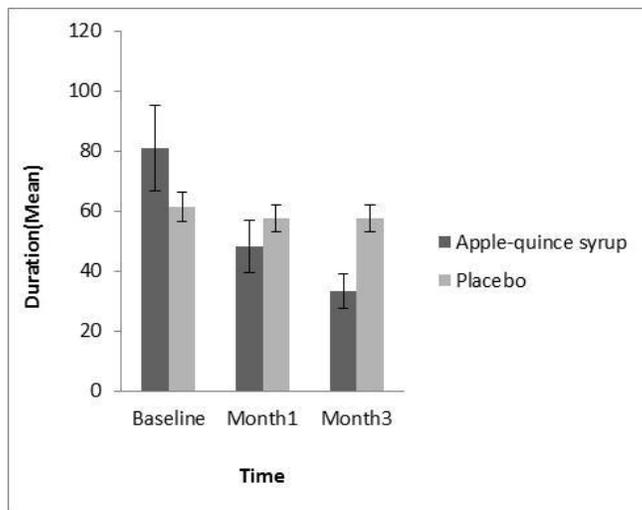


Figure 3: Duration of migraine headache attacks at various time points

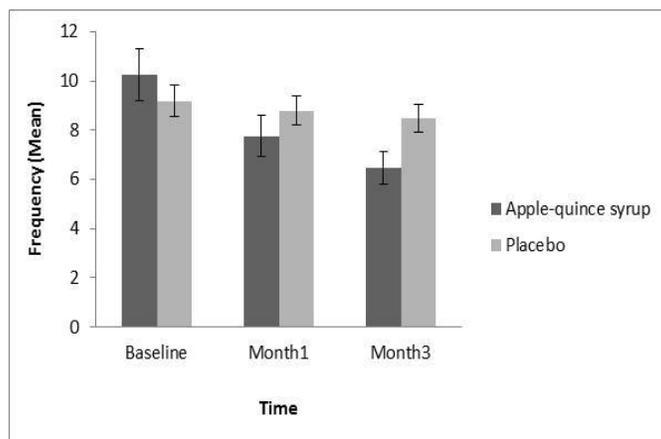


Figure 4: Frequency of migraine headache attacks at various time points

DISCUSSION

This was the first trial on the effect of apple-quince syrup on the severity of pain (VAS score after one month and after 3 months of intervention) in patients with migraine headache. The main findings of the study was beneficial effect of apple-quince syrup on all parameters of the migraine headache (frequency, severity and duration of the attack), compared to placebo syrup. Migraine is known as a common health problem with a great impact on daily activities and social functioning. Migraine attacks are usually unilateral and severe pulmonary headaches that last 4 to 72 hours. These headaches are usually accompanied by vomiting and photophobia (Marmura et al. 2015). Previous studies have shown that more than 50% of migraine has a genetic etiology, but other epigenetic mechanisms are also suggested for the disease (Dodick and Silberstein, 2006). The pathophysiology of this common nerve-vascular disease has many aspects and has not been fully understood yet. The neuronal theory, peripheral and central sensitivity, and the low levels of 5-hydroxytryptamine (5-HT) in the central nervous system lead to increase the incidence of migraine attacks (Dodick et al. 2006). From possible pathogenesis of the disease is neurogenic meninges inflammation, which is due to rising cytokines during migraine attacks (Olesen et al. 2009). Cytokines activate special neuronal pathways for transmitting pain signals to trigeminovascular system and vegetative nervous system (VNS) nuclei. These conditions are susceptible to disruption of the VNS function, and ultimately lead to headaches (Fidan et al. 2006). Some studies have shown that abnormal signaling pathways of nitric oxide (NO) and its synthesis may also be considered as an inflammatory factor in the pathophysiology of the disease (Neri et al. 2015). Thus, three known pathogenesis of migraine headache include dysfunctional nervous structures, inflammatory condition and functional alteration of the VNS (Olesen et al. 2009). Many healing therapies are based on relief and reduced excitement of the central nervous system. Anti-inflammatory therapies have also been introduced as another treatment option (Affaitati et al. 2017). Based on the recommendation of the American Headache Association, a preventive treatment should follow three main objectives: 1) Reduction in frequency, severity and duration of headache. 2) Improvement of responsiveness to acute

attacks. 3) Improvement and increase in the function and reduction in the patient's disability (Marmura et al. 2015). The results of previous clinical trials on chemical drugs have frequently reported adverse side effects. In several studies done on propranolol, which is considered a category of beta-blocker drugs, symptoms such as decreased consciousness, excessive fatigue, sleep disorders, nightmares, depression and memory impairment have been observed (Linde and Rossnagel, 2004).

Some studies have been conducted to identify helpless and uncomplicated herbal medicines, which has the therapeutic effect of chemical drugs. Jafarpour et al. (2016) studied 90 patients with migraine headaches. They divided patients into three treatment groups of citron syrup, propranolol and placebo. Thirteen patients received 15 ml Citron Syrup 3 times a day for 4 weeks. In the two other therapeutic groups, the same amount of placebo and 20 mg of Propranolol tablet were used respectively. At the end of the trial, compared to placebo, Citron Syrup significantly reduced the severity of migraine headaches (MD: 2.97; 95%CI: (2.07, 3.86]) vs. (MD: 0.83; 95%CI: (-0.027, 1.69]). However, the severity of pain reduction in the citron syrup treatment group was greater than the propaneal group. However, no significant difference was observed between the two groups (MD: 2.97; 95% CI: (2.07, 3.86]) vs. (MD: 2.58; 95% CI: (1.59, 3.57]).

In another study, by Delvar Kasmaei et al. (2016) in 2014, on 68 patients with migraine, the effect of coriandrum sativum syrup on the severity, duration and frequency of the disease was examined. The mean duration, severity and frequency of migraine headaches was significantly lower in the treatment group by 50% than the control group.

In crossover trial conducted in March 2007 to March 2008 to evaluate the efficacy and safety of menthol 10% solution in Namazi Hospital, Shiraz, Iran, eligible participants were divided into 2 groups of 60 patients with 10% menthol and the placebo group. The solution was rubbed on the patient's forehead and temple. In the menthol group, 58.3% of patients and in the placebo group 17.2% of the patients recovered 2 hours after rubbing the drug. After 24 hours, 33.3% of patients in the menthol group and 12.1% of patients in the placebo group reported improvement. The researchers concluded that menthol solution is safe and effective in treating migraine (Borhani et al. 2018). In several studies

focused on herbal remedies, all had achieved favorable results (Jafarpour et al. 2016; Kasmaei et al. 2016; Fu et al. 2012; Cady et al. 2011; Borhani et al. 2008). In addition to herbal remedies, other therapies for complementary medicine have also been studied in previous studies. In these studies, favorable results from cupping, acupuncture and yoga have been obtained for the treatment of the frequency, severity and duration of migraine headaches (Ahmadi et al. 2008; John et al. 2007; Li et al. 2009; Wang et al. 2011). According to Iranian medicine principles, fragrant medicines strengthens the soul and organ, and also lead to the survival of life. These are used in the treatment of brain diseases and the nervous system, including headaches (Abokrysha, 2009).

Cydonia Oblonga M., a medicinal plant of family Rosaceae, is used to treat some ailments such as cancer, diabetes, hepatitis, ulcer, respiratory, and urinary infections, etc. (Etebari et al. 2015). Quince or *Cydonia oblonga* is in useful secondary metabolites such as phenolics, steroids, flavonoids, terpenoids, tannins, sugars, organic acids, and glycosides. Activities like antioxidant, antibacterial, antifungal, anti-inflammatory, hepatoprotective, cardiovascular, antidepressant, antidiarrheal, hypolipidemic, diuretic, and hypoglycemic have been attributed to *C. oblonga* (Silva et al. 2004; Hamazu et al. 2005).

Silva et al. performed qualitative and quantitative research on quince fruit (pulp and peel) collected from different regions of Portugal. They evaluated their antioxidant potential using DPPH assay. It was observed that phenolic fractions possessed strong free radical scavenging activity than that of organic acid fractions and whole methanolic fractions (Papp et al. 2013). Phenolic composition of fruit and its antioxidant ability revealed clear evidence of its medicinal importance. Papp et al. compared phenolic profile and antioxidant potential of Quince peel and fruit of 12 different cultivars and drived that fruit is a rich source of phenolics with strong antioxidant activity. The cultivars such as "Champion," "De Husi," and "Konstantinapolyi" were known best for scavenging free radicals. The analysis of phenolic contents of aqueous alcoholic extracts using Folin-Ciocalteu reagent depicted appreciable amounts of phenolics (8.55mg GAE/g FW) in fruit (Fattouch et al. 2007). It was observed that peel has higher radical scavenging activity than pulp (Fattouch et al. 2007). Anti-inflammatory and anti-allergic role of Quince fruit peel phenolic

has been studied after aggravating inflammation in human THP-1 cell line through lipopolysaccharide (LPS). Quince fruit peel extract significantly inhibited the release of inflammatory mediators such as cytokines (TNF- α) and interleukins (IL-8) by inducing release of Interleukin-10 and Interleukin-6 from mast cells (Essafi-Benkhadir et al. 2012). Apple (*Malus domestica* Borkh.), which is a member of the family Rosaceae, is one of the most frequently consumed fruits in many regions worldwide. Apple fruit has been identified as an excellent potential source of carbohydrates, minerals, dietary fiber and antioxidant phenolic (Veberic et al. 2005).

Recent studies reveal that consumption of apple fruit and apple juice can give antiproliferative, anticarcinogenic and anti-inflammatory health benefits and is strongly associated with lower incidence of lung cancer, viral diseases and cardiovascular disorders. Apple peel is also useful for its medicinal health functions (Manzoor et al. 2012). Phenolic compounds clean free radicals and inhibit their production, stimulate the synthesis of antioxidant enzymes

, and thus arrest oxidative stress resulting in damage to the structural molecules of the body (Cai et al. 2004).

According to the following reasons, apple-quince syrup can be a hypothesis for the development of a natural medicine to treat migraine. Nitric Oxide is a critical molecule may be with migraine headaches. Migraine attacks and pain is reducible by blockade of its synthesis (Ashraf et al. 2016). NO is effective in stimulating central sensitization. Then, NO synthase (NOS) inhibition has an important role in treating migraine (Neri et al. 2015). Phenolic compounds inhibit NOS expression in activated macrophages and prohibition of NO release and synthesis occurs. Moreover, it can minimize inflammation at the site of action and decrease migraine pain (Costa et al. 2015). It seems that phenolic compounds are associated with strong inhibitory effect on endogenous prostaglandin E₂ (PGE₂) levels in RAW 264.7 macrophages. It is a selective COX-2 inhibitor and relieves anti-inflammatory and pain relief effects (Antonova et al. 2013). COX-2 inhibitors can blocked and stopped the central neurons and the peripheral meningeal nociceptors sensitizations. It may be similar to NSAIDs, such as Naproxen and Ibuprofen without their adverse GI effects (Silberstein and strip, 2014; Li et al. 2017)

CONCLUSION

Apple-quince syrup is a safe and effective intervention as a first-line abortive treatment for migraine patients that experience mild headache prior to the onset of moderate to severe headache. It appears to be well tolerated and has no known contraindications with other acute treatments for migraine.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest in the present study.

ACKNOWLEDGEMENT

The authors would like to thank the Clinical Research Development Unit of Baqiyatallah Hospital, for all their support and guidance during carrying out this study.

AUTHOR CONTRIBUTIONS

FA and MM designed the trial and AK and HM performed data collection and analysis. JHN wrote and reviewed the manuscript. All authors read and approved the final version.

Copyrights: © 2021@ author (s).

This is an open access article distributed under the terms of the [Creative Commons Attribution License \(CC BY 4.0\)](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

REFERENCES

- Abokrysha N. (2009). Ibn Sina (Avicenna) on pathogenesis of migraine compared with the recent theories. *Headache: The Journal of Head and Face Pain* 2009;49:923-927.
- Affaitati G, Martelletti P, Lopopolo M, Tana C, Massimini F, Cipollone F, Lapenna D, Giamberardino MA, Costantini R. (2017). Use of Nonsteroidal Anti-Inflammatory Drugs for Symptomatic Treatment of Episodic Headache. *Pain Practice*;17:392-401.
- Ahmadi A, Schwebel DC, Rezaei M. (2008). The efficacy of wet-cupping in the treatment of tension and migraine headache. *The American journal of Chinese medicine* .36:37-44.
- Al-Snafi AE: The medical importance of *Cydonia oblonga*-A review. *IOSR Journal of Pharmacy* Antonova M, Wienecke T, Olesen J, Ashina M. (2013). Prostaglandin E2 induces immediate migraine-like attack in migraine patients without aura. *The journal of headache and pain*. 14:P113.
- Ashraf MU, Muhammad G, Hussain MA, Bukhari SNA: *Cydonia oblonga* M., A . (2016). medicinal plant rich in phytonutrients for pharmaceuticals. *Frontiers in pharmacology*;7.
- Borhani HA, Motazedian S, Pourmokhtari S, Khodaei S, Mohammadi F, Rezaei R, Salarian L, Shirvani Z, Ziaei AR, Hekmati S. (2008). Cutaneous application of Menthol 10% solution on temporal area in acute treatment of common migraine. *Medical journal of Hormozgun university*;12:83-88.
- Burch RC, Loder S, Loder E, Smitherman TA. (2015). The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache: The Journal of Head and Face Pain*;55:21-34.
- Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, Fanning KM, Serrano D, Lipton RB. (2013). Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache: The Journal of Head and Face Pain*;53:1278-1299.
- Cady RK, Goldstein J, Nett R, Mitchell R, Beach ME, Browning R. (2011). A Double-Blind Placebo Controlled Pilot Study of Sublingual Feverfew and Ginger (LipiGesticTMM) in the Treatment of Migraine. *Headache: The Journal of Head and Face Pain*;51:1078-1086.
- Cai Y, Luo Q, Sun M, Corke H. (2004). Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. *Life sciences*;74:2157-2184.
- Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. (2015). Trends in the use of complementary health approaches among adults: United States, National health statistics reports:1.
- Costa DC, Costa HS, Albuquerque TG, Ramos F, Castilho MC, Sanches-Silva A. (2015). Advances in phenolic compounds analysis of aromatic plants and their potential applications. *Trends in Food Science &*

- Technology;45:336-354.
- Diener H-C, Dodick DW: Headache research in 2015. (2016). progress in migraine treatment. *The Lancet Neurology*;15:4.
- Dodick D, Silberstein S. (2006). Central sensitization theory of migraine: clinical implications. *Headache: The Journal of Head and Face Pain*;46.
- Essafi-Benkhadir K, Refai A, Riahi I, Fattouch S, Karoui H, Essafi M. (2012). Quince (*Cydonia oblonga* Miller) peel polyphenols modulate LPS-induced inflammation in human THP-1-derived macrophages through NF- κ B, p38MAPK and Akt inhibition. *Biochemical and biophysical research communications*;418:180-185.
- Etebari M, Zolfaghari B, Jafarian-Dehkordi A. (2015). Evaluation of genoprotective effects of hydroalcoholic and polyphenolic extracts of Quince by comet assay. *Journal of Reports in Pharmaceutical Sciences (J Rep Pharm Sci)*;4:141-147.
- Fattouch S, Caboni P, Coroneo V, Tuberoso CIG, Angioni A, Dessi S, Marzouki N, Cabras P. (2007). Antimicrobial activity of Tunisian quince (*Cydonia oblonga* Miller) pulp and peel polyphenolic extracts. *Journal of Agricultural and Food Chemistry*;55:963-969.
- Fidan I, Yuksel S, Ymir T, Lrkec C, Aksakal FN. (2006). The importance of cytokines, chemokines and nitric oxide in pathophysiology of migraine. *Journal of neuroimmunology*;171:184-188.
- Fu C, Yu L, Zou Y, Cao K, Zhao J, Gong H, Zhang S, Lin A, Dong M, Yang W. (2012). Efficacy of chuanxiong ding tong herbal formula granule in the treatment and prophylactic of migraine patients: a randomized, double-blind, multicenter, placebo-controlled trial. *Evidence-Based Complementary and Alternative Medicine*.
- Gorji A. (2003). Pharmacological treatment of headache using traditional Persian medicine. *Trends in pharmacological sciences*;24:331-334.
- Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. (2012). Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*;78:1346.
- Hagen SF, Borge GIA, Bengtsson GB, Bilger W, Berge A, Haffner K, Solhaug KA. (2007). Phenolic contents and other health and sensory related properties of apple fruit (*Malus domestica* Borkh., cv. Aroma): Effect of postharvest UV-B irradiation. *Postharvest Biology and Technology*;45:1-10.
- Hamazu Y, Yasui H, Inno T, Kume C, Omanyuda M. (2005). Phenolic profile, antioxidant property, and anti-influenza viral activity of Chinese quince (*Pseudocydonia sinensis* Schneid.), quince (*Cydonia oblonga* Mill.), and apple (*Malus domestica* Mill.) fruits. *Journal of Agricultural and Food Chemistry*;53:928-934.
- John PJ, Sharma N, Sharma CM, Kankane A. (2007). Effectiveness of yoga therapy in the treatment of migraine without aura: a randomized controlled trial. *Headache: The Journal of Head and Face Pain*;47:654-661.
- Kasmaei HD, Ghorbanifar Z, Zayeri F, Minaei B, Kamali SH, Rezaeizadeh H, Amin G, Ghobadi A, Mirzaei Z. (2016). Effects of *Coriandrum sativum* Syrup on Migraine: A Randomized, Triple-Blind, Placebo-Controlled Trial. *Iranian Red Crescent Medical Journal*;18.
- Li C, Zhu Q, He Q, Wang J, Wang F, Zhang H. (2017). Plasma Levels of Cyclooxygenase-2 (COX-2) and Visfatin During Different Stages and Different Subtypes of Migraine Headaches. *Medical science monitor: international medical journal of experimental and clinical research*;23:24.
- Li Y, Liang F, Yang X, Tian X, Yan J, Sun G, Chang X, Tang Y, Ma T, Zhou L. (2009). Acupuncture for treating acute attacks of migraine: a randomized controlled trial. *Headache: The Journal of Head and Face Pain*;49:805-816.
- Linde K, Rossnagel K. (2004). Propranolol for migraine prophylaxis. *The Cochrane Library*.
- Jafarpour M, Yousefi G, Hamed A, Shariat A, Salehi A, Heydari M. (2016). Effect of a traditional syrup from *Citrus medica* L. fruit juice on migraine headache: A randomized double blind placebo controlled clinical trial. *Journal of ethnopharmacology*;179:170-176.
- Marmura MJ, Silberstein SD, Schwedt TJ. (2015). The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache: The Journal of Head and Face Pain*;55:3-20.
- Mentz RJ, Hernandez AF, Berdan LG, Rorick T, O'Brien EC, Ibarra JC, Curtis LH, Peterson ED. (2016). Good Clinical Practice Guidance and Pragmatic Clinical Trials.

- Circulation;133:872-880.
- Mahdizadeh S, Ghadiri MK, Gorji A. (2015). Avicenna's Canon of Medicine: a review of analgesics and anti-inflammatory substances. *Avicenna journal of phytomedicine*;5:182.
- Malik R, Freilinger T, Winsvold BS, Anttila V, Vander Heiden J, Traylor M, De Vries B, Holliday EG, Terwindt GM, Sturm J. (2015). Shared genetic basis for migraine and ischemic stroke A genome-wide analysis of common variants. *Neurology*;84:2132-2145.
- Manzoor M, Anwar F, Saari N, Ashraf M. (2012). Variations of antioxidant characteristics and mineral contents in pulp and peel of different apple (*Malus domestica* Borkh.) cultivars from Pakistan. *Molecules*;17:390-407.
- Nahin RL, Boineau R, Khalsa PS, Stussman BJ, Weber WJ. (2016). Evidence-based evaluation of complementary health approaches for pain management in the United States: Mayo Clinic Proceedings, Elsevier, 91, pp 1292-1306.
- Neri M, Frustaci A, Milic M, Valdiglesias V, Fini M, Bonassi S, Barbanti P. (2015). A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. *Cephalalgia*;35:931-937.
- Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. (2009). Origin of pain in migraine: evidence for peripheral sensitisation. *The Lancet Neurology*;8:679-690.
- Orr SL, Friedman BW, Christie S, Minen MT, Bamford C, Kelley NE, Tepper D. (2016). Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies. *Headache: The Journal of Head and Face Pain*;56:911-940.
- Papp N, Szabo T, Szabo Z, Nyeki J, Hegedus A. (2013). Antioxidant capacity and total polyphenolic content in quince (*Cydonia oblonga* Mill.) fruit. *International Journal of Horticultural Science*;3:33-35.
- Sajid SM, Zubair M, Waqas M, Nawaz M, Ahmad Z. (2015). A Review on Quince (*Cydonia oblonga*): A Useful Medicinal Plant. *Global Veterinaria*;14:517-524.
- Silberstein SD, Stirpe JC. (2014). COX inhibitors for the treatment of migraine. *Expert opinion on pharmacotherapy*;15:1863-1874.
- Silva BM, Andrade PB, Valentão P, Ferreres F, Seabra RM, Ferreira MA. (2004). Quince (*Cydonia oblonga* Miller) fruit (pulp, peel, and seed) and jam: antioxidant activity. *Journal of Agricultural and Food Chemistry*;52:4705-4712.
- Smitherman TA, Burch R, Sheikh H, Loder E. (2013). The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache: The Journal of Head and Face Pain*;53:427-436.
- Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, Dias S, Schulz KF, Plint AC, Moher D. (2012). Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *The Cochrane Library*.
- Veberic R, Trobec M, Herbinger K, Hofer M, Grill D, Stampar F. (2005). Phenolic compounds in some apple (*Malus domestica* Borkh) cultivars of organic and integrated production. *Journal of the Science of Food and Agriculture*;85:1687-1694.
- Wang L-P, Zhang X-Z, Guo J, Liu H-L, Zhang Y, Liu C-Z, Yi J-H, Wang L-P, Zhao J-P, Li S-S. (2011). Efficacy of acupuncture for migraine prophylaxis: a single-blinded, double-dummy, randomized controlled trial. *PAIN*;152:1864-1871.
- Zargaran A, Borhani-Haghighi A, Faridi P, Daneshamouz S, Mohagheghzadeh A. (2016). A review on the management of migraine in the Avicenna's Canon of Medicine. *Neurological Sciences*;37:471-478.