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Review Article

CONSTIPATION AND HEADACHE RELATIONSHIP: A NARRATIVE REVIEW ON PERSIAN MEDICINE TEXTS AND MODERN LITERATURE

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Abstract:

Objective: Headache is a common cause of visits to health care centers. According to World Health Organization Forum, migraine alone is the seventh cause of disability among all diseases. This article attempts to highlight the importance of normal bowel movement in management of headache symptoms.

Methods: This study was carried out with searching through traditional books using keywords 'Sodaa' (headache) and 'Yobusat' (constipation) in Noor software, while search in modern medicine literature was performed using Medline(PubMed) and Scopus databases and Persian medical databases such as SID, with keywords "headache", "migraine", "constipation", "gastrointestinal" and "autonomic". Insufficient attention to underlining factor of headache was limitation in mentioned studies. Finally, studies evaluating the comorbidity of these two disorders were selected.

Results: According to Persian medicine texts, constipation is considered one of the important factors for onset or exacerbation of headache. As well, the results obtained from studies in modern medicine, relatively confirmed this relationship and demonstrated a close association between constipation and headache (especially non migraine headache).

Conclusion: In Persian medicine, constipation is one of the most important predisposing factors for headaches and the results achieved from modern literature in this study, suggested that constipation might be considered as a contributing factor; however, more researches are needed to clarify the relationship between headache and constipation. Therefore, considering the importance of treating constipation, use of medicines with no constipation as a side effect or use of traditional medicine laxatives along with the conventional treatment might be suggested.

Keywords: Headache, Constipation, Persian Medicine, Modern Medicine.

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INTRODUCTION:

The term headache generally refers to the existence of pain in the head. This disorder is accompanied by a number of disabling complications and ranked as one of the most common disorders in the world [1]. Based on the third edition of the international classification of headache disorders (ICHD-III, beta version), which was published in 2013, there are generally two classifications of headaches: Primary headaches including migraine, tension-type headache, trigeminal autonomic cephalalgia and other primary headache disorders; Secondary headaches referring to headaches that occur due to an underlying cause such as trauma or injury to the head/neck, cranial or cervical vascular disorder, abuse of a substance or its withdrawal, infection, and psychiatric disorders. It is obvious that successful treatment of this latter category of headaches depends on curing the underlying cause [2]. Complications of medicines used for management of headaches such as constipation [3, 4], HTN [5] and depression [6] are inevitable. Moreover, a World Health Organization study shows a global neglect towards headaches [7, 8] and has recommended the use of traditional medicines to find new complementary treatments [9].

Persian Medicine (PM) is a type of traditional medicine in the Middle East with a history of more than thousand years. A number of studies confirmed the efficacy of traditional medicine for migraine [10-13]. In this system of medicine, preservation of health depends on appropriate lifestyle which is described as six essential health factors in PM. They include: exercise and physical activity, food and drink, sleep and wakefulness, air and climate, mental state, and finally accumulation and expulsion. In this system of medicine, the subject of bowel movement is discussed under the topic of accumulation and expulsion of consumed foods. If the bowel movement is not regular, the individual gradually develops accumulation [14-16].

Persian scholars such as Avicenna (*Ibnesina*, 980-1037 AD) and Rhazes (*Razi*; 854-925 AD), have mentioned 28 varieties of headache and the term “soda’a” is used to explain headache. Avicenna, is considered one of the greatest physicians in traditional medicine history. He explained the etiology and symptoms of headache, in the third volume of the *Al-Qanoon-Fil-Teb* (Canon of Medicine), and described that the main cause of pain is one of these factors: Distemperament of the organ, Disruption of anatomical structure and both of these factors.

In addition, Avicenna classified kinds of headache from different perspectives. For example, based on

location of pain: pain of frontal or occipital region or based on the organ of origin, headache divided into two type:

-The main headache: in this type, the pathology is located in the head such as CNS or vascular.

-“Participatory Headache”: is one type of them which can occur due to dysfunction of organ except brain and has several subtypes such as “Headaches of Gastrointestinal Origin”, for instance due to constipation [17, 18]. Constipation is the first and most important headache underlying factors mentioned in treatment guidelines of PM [18, 19, 17].

The definition of normal defecation in PM has a wide domain, because it has explained features such as the daily passage of soft stool without any pain or discomfort or a “*borborygmi*” or foamy material on the stool plus appropriate color and volume [20].

Constipation is a global issue that has an impact on quality of life in various populations with a collective prevalence about 22.5 percent in Europe and Oceania; the corresponding figure is lower in Asian countries such as Korea and Iran [21-23]. The disorder is defined as infrequent passage of feces and or hard stool and a sense of incomplete emptying after defecation. Chronic constipation may lead to several adverse outcomes including decreased appetite, feeling pain [24].

Persian scholars believed that constipation can lead to several ailments such as infectious diseases, plethora and others [16, 25]. On the other hand, headache can be exacerbated by accumulation of wastes and harmful material in the body [14] and constipation, as one of the main causes of this process, demands more attention. Although the co-morbidity of headaches and upper GI problems have been the backbone of several researches during previous years [26-28]; there are few surveys available evaluating headache and constipation simultaneously [28, 26, 27, 29], and yet there is no established casual association between headache and constipation in modern text. In this study, we reviewed the recent studies of current medicine researches as well as Persian medicine texts in the field of constipation and headache, suggesting the importance of this association as a potential source for future investigations and management of headache.

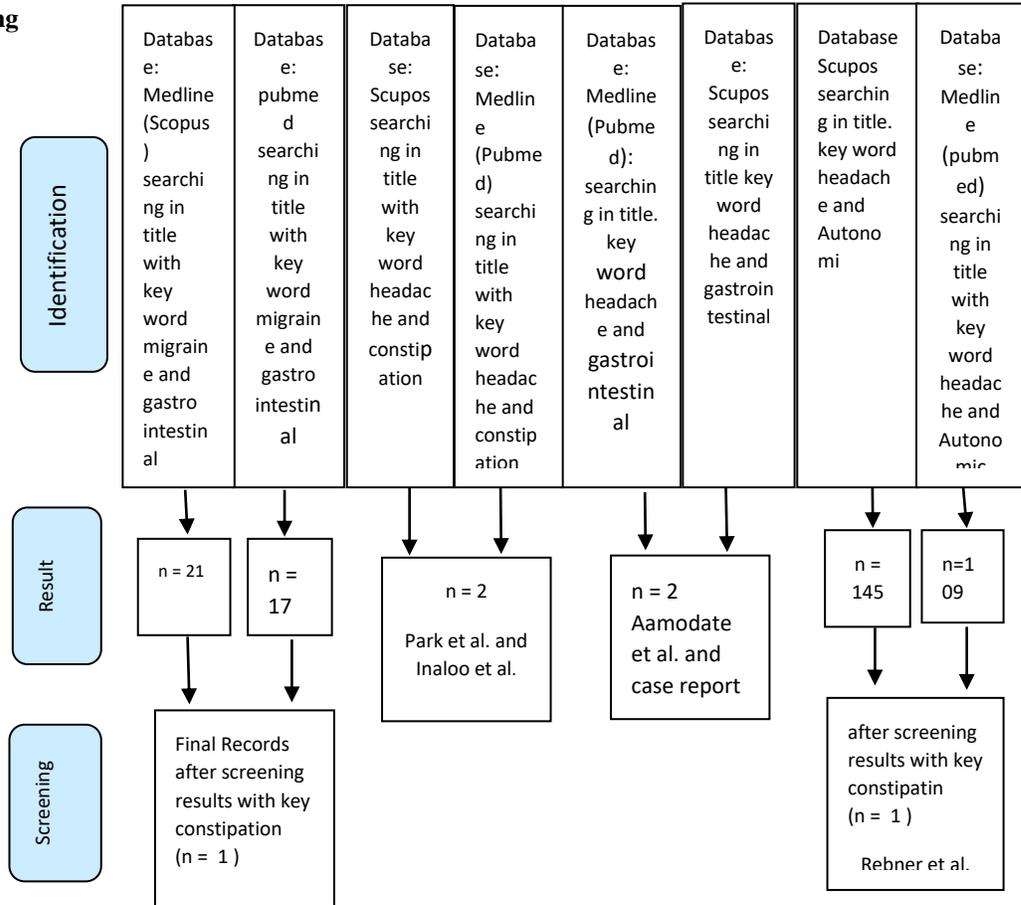
Methods

First of all, we searched traditional medicine sources, the keywords ‘*Sodaa*’ (headache) and ‘*Yobusat*’ (constipation) were used for conducting a search using a comprehensive software in the field of traditional Medicine named Noor digital library. This software covers a vast range of topics in medicine, including the

most ancient medical texts, then we searched the clinical trails and observational articles in Medline(Pub Med) and Scopus databases, Persian database such as SID, using keyword i.e. “headache”, “migraine” and

“constipation”, “gastrointestinal”, “autonomic” in title and in the period between 2000 to July 2017.

Flow diagram searching



Studies with non-related subjects were removed and only those with simultaneous evaluation of constipation and headache were selected. Finally, six articles were found evaluating headache and constipation at the same time and explaining a relationship between these two comorbidities [29, 27, 26, 30].

Results in traditional medicine

Persian scholars such as Avicenna in *Al-Qanoon-Fil-Teb* (Canon of Medicine) and Rhazes in *Al-Havi* (Liber Continent), have mentioned 28 varieties of headaches. “Participatory Headache” is one type of them which can occur due to dysfunction of organ except brain and has several subtypes such as “Headaches of GI Origin”. Accumulation of wastes and harmful materials in GI disorders such as constipation, can induce “Headaches of GI Origin”. In other words, Persian scholars assumed constipation, as a predisposing factor for headache, so the treatment of constipation was the first therapeutic step in all diseases such as headache [18, 17].

In PM, constipation and headache have a two-way communication; in other words, we can say that not only constipation can cause or aggravate headaches, but headaches sometimes cause or aggravate constipation [28, 14]. Persian scholars have described the attributes of a normal bowel habit in detail. *Jorjani* in *“Alaghrza Altebyeh va Almabahesa al alalaeia”*, believes that human stool and the defecation process are normal when the following features are present:

- “Appearance: It must be similar in different segments of one fecal product.
- Fecal odor: it should be neither malodorous nor odorless.
- Quantity and volume: it should be in proportion with the food taken, not less or more in weight and volume.
- Color: it should be light yellow at all times, except when colored food is consumed
- Consistency: it should be neither too thick nor too loose (with the consistency of honey).

- Time of defecation: fecal excretion should appear approximately 12-24 hours after eating.
- Defecation should occur spontaneously and without any strain.
- No rush or force should be involved in the process.
- Defecation should not be accompanied with *borborygmi*.
- Stool should not be foamy "[31, 20].

Rhazes in *Al-Havi* (Liber Continent) and other traditional scholars mentioned that even in the absence of complaints related to constipation, using laxatives and stool softeners can lead to more successful management of disease, such as using *Golghand'* [32] in weakness ("Zaa'f") of the brain. Weakness of the brain is the principal reason of the brain's inefficiency to remove waste materials, and chronic headaches or existence of diseases in other organs of the body such as stomach, chronic pain and inappropriate lifestyle, especially constipation can trigger it. Weakness of the brain is an important cause of headache in PM [18, 19, 16]. That is why most drugs used in PM for headache management, have some laxative components [33, 18].

Results in modern medicine

Although, scientific literature depicting the simultaneous presence of headaches and constipation is rare, our search led us to the following studies: One of the first studies reported the possible relationship between headache and constipation was a case report about the coincidence of the disorders published in Birmingham in 2002. In the study, a 47 year old female patient with chronic constipation was reported to be suffering from headaches. She used more fruits and vegetables as well as fiber in her diet to control constipation, which led to relief of her constipation and finally reduced the frequency of the headaches [30].

In 2008, Aamodt et al. reported higher prevalence of headache among individuals who suffered from chronic constipation (OR 2.1, 95% CI 1.9, 2.4), compared with those without this problem. They used a questionnaire to this end. Therefore, constipation may be considered an aggravating factor for headache [26].

Inaloo et al. (2012), in their cross-sectional study conducted in Shiraz, Iran, interviewed the subjects and their parents using a structured questionnaire towards diagnosing constipation and headache. In their study, 326 children were randomly divided into two groups: one group included children who referred to the gastroenterology clinic due to the chief complaint of constipation (based on Rome III criteria) and the other group contained healthy school children. Then, they evaluated the prevalence of headache (according to the international classification of headache disorders [ICHD-II]) in the both

groups. The results revealed significantly higher prevalence of headache in the group with constipated children (19.8%) as compared to the other group (5.6%), [Odds ratio (OR) 4.192, $p < 0.001$], being meaningful only in the non-migraine headache subtypes (15.1% vs 2.8%, OR 25, $p < 0.002$) [27].

In another study conducted in the Department of Pediatrics of a South Korean hospital, information on headache and constipation was collected by completing a questionnaire for each patient. In this study, 96 children with headache (ICHD II) were divided into two groups: one group with comorbid constipation in 25% (Rome III) and the other group without it. They were followed for 100 days and the first group received treatment for constipation as well. The group receiving treatment for constipation showed more improvement in terms of headache symptoms [29].

A retrospective study conducted by Rabner et al. in Boston, the United States, 231 patients aged 5–18 years were recruited. The patients were allocated to three groups, i.e., diagnosed with migraine, tension-type headache (TTH), and idiopathic scoliosis (IS) as the control group, as IS does not typically show the symptoms of CNS autonomic dysfunction. The control group underwent evaluation and diagnosis in an orthopedic clinic. In addition, in both the headache groups, (based on ICHD-2 classifications), clinical notes from the patients' initial data were evaluated by a pediatric neurologist. Moreover, the presence of symptoms indicating autonomic dysfunction was examined using the COMPASS31 checklist. Constipation was defined as no bowel movements for more than 2 days; or difficulty, straining in defecation. The rate of constipation among the patients suffering from migraine, TTH and IS was 7%, 18% and 5% respectively. Significant difference was found between the groups ($p < 0.001$). They reported that although the observed disability may be related to the autonomic nervous system, future research may need to clarify why constipation may be higher in pediatric TTH than in migraine [34].

In a case-control study carried out by Julie Le Gal et al. in France and Italy, 1072 participants, aged 6–17 years, were divided into two groups: 648 participants were considered as the control group with no primary headache and 424 participants as cases (257 patients with migraine and 167 with tension-type headache). Multivariable logistic regression showed that there was an inverse association between migraine and functional constipation only for adolescents (0.34, 0.14–0.84, $p = 0.02$) and functional constipation was less prevalent in the participants with migraine than in those in the control group. Furthermore, no significant association

was noted between functional constipation disease and

However, there is no explanation for the inverse

Table 2: Results of the Studies Evaluating the Relationship Between Headache and Constipation in Modern Medicine

| Study/ Year of publication | Sample size/ Country | Age | Type of Study/ measuring instrument | Results and Conclusion |
|----------------------------|--------------------------------|-----------------------|---|---|
| Egilius L.H (2002) | 1(Birmingham) | A 47 years old female | A case report study/ Questionnaire | It appears that the constipation may contribute to headache and can trigger it. She used more fruits and vegetables as well as fiber in her diet to control constipation, which led to relief of her constipation and finally, reduced the frequency of the headaches. |
| Aamodt et al. (2007) | 43,782 (Norway) | Adult age>20y/ o | Cross-sectional Study/ Questionnaire | Prevalence of headache was higher in the constipated patients; in addition, constipation increased significantly with increasing headache frequency. There were no major differences in the relationship between migraine and tension headache with constipation. |
| Inaloo et al. (2014) | 326 (Iran) | 4-12 years old | Cross-sectional study/ Questionnaire | As children emotional stress can trigger both headache and GI problems, more researches are needed. There is a strong correlation between non-migraine subtype headache and chronic functional constipation. |
| Park et al. (2015) | 96 (Korea) | 125.9±40.2 months | Retrospective study/ Questionnaire | There may be a relationship between constipation and headache. Resolution of constipation improves headache situation (tension headache being the majority of them). |
| Rabner et al. (2016) | 231 (Boston) | 5-18 years old | A retrospective study/ Questionnaire | More researches on autonomic dysfunction in pediatric headache are needed. There was a close correlation of constipation with tension-type headaches . |
| Julie Le Gal et al. (2016) | 1072 (France and Italy) | 6- 17 years old | A case-control study/ Questionnaire | There was a negative association for functional constipation with migraine . There was no explanation for this inverse relationship with constipation, and future studies should explore this finding. There was also no significant association between functional constipation disease and tension-type headaches |

tension-type headaches (1.03, 0.52- 2.03, p=0.94).

relationship with constipation, and more future studies are needed to explore this finding [35].

DISCUSSION:

In general, our primary assessments through Persian medicine literature showed a strong association between constipation and headache. This fact was further confirmed by modern medicine (five of the six papers in present studies). Results obtained from published documents in two papers have shown the alleviation or relief of headaches after the treatment of concomitant constipation [29, 30].

Although Upper GI problem have more incidence in migraine patients, our study indicated a close relationship between non migraine headache and constipation. It seem that complicated causes of headache and underlying factors were limitation of mentioned studies, for example due to migraine and multifactorial pathogenesis, migraine headache is treated based on precise individualized examination. To achieve the best treatment goal, all other accompanied conditions such as psychiatric disorders and GI related problems should be identified [36] and included in the questionnaire. This requires exact identification of the disease development and its related comorbidities [37], such as individual distemperament of brain, psychiatric disorders and GI related problems to assign a suitable questioner, it seem that invalid questioner were limitation for some studies such as Rabner *et al.*, Park *et al.* and Aamodt *et al.* and retrospective study and cross sectional type of studies were another limitations of studies. In this study most of papers have indicated a positive relationship between headache (especially tension headache) and constipation, despite the study by Julie Le Gal, in which a negative relationship has been mentioned between migraine headache and constipation and we do not have explanation for this result. These results raise the idea of the existence of a possibly unique diagnostic entity in the classification of headache disorders, the "Headache of GI Origin." [18, 17].

Regarding accompanied comorbidities, it has been reported that migraine is associated with a number of GI related problems such as constipation, diarrhea, dyspepsia, celiac disease, gastro esophageal reflux (GERD), and irritable bowel syndrome (IBS) [38].

CGRP antagonist drugs and tricyclic antidepressant agents can be beneficial in migraine prevention [39], however, constipation is a side effect of some of the mentioned drugs [3, 21]. The role of autonomic dysfunction in migraine pathophysiology and its link with GI disorders has been explored in the previous researches. [38, 26].

In addition, both constipation and headache might have a relation with serotonin function, and might worsen with stress, dehydration and loss of appetite. Furthermore, Valsalva maneuver usually increases the

headache severity during the migraine attack. On the other hand, constipation can also aggregate Valsalva maneuver, which may eventually lead to severe headache attacks in individuals suffering from migraine [29, 38, 26, 40-43].

Furthermore, it has been suggested that inflammatory state in the trigeminovascular system may influence the progression of migraine headache. It is worthwhile that the severity of this state can be affected by inflammation and immune state of the GI system [38]. Due to the bidirectional connection between the gut and the brain through different neurological, immunological and endocrine mechanisms (which is known as gut-brain axis), it is now widely suggested that microbiota of the GI tract can influence a number of brain related disturbances including headaches, especially migraine [38]. On the other hand, the disturbed profile of gut microbiota may be involved in pathogenesis of chronic constipation [24].

Gut microbiome alteration and changes in immunity of the GI tract can produce inflammatory mediators that play a role in stimulation of the trigeminovascular system, leading to aggravation of migraine. Furthermore, the microbiome can cause GI motility disorders and constipation; This can even lead to gastric stasis or headaches in the long term. [39, 38, 44].

Thus, modifying the microbiota through improving dietary intakes and attenuating inflammation positively affects the gut-brain axis and any disturbances associated with each of the organs such as chronic constipation and migraine headache [38, 39].

The effect of gut microbiota on headache in modern medicine may be comparable to the PM view, in which the GI problem such as constipation, may worsen headaches' symptoms.

Thus, based on the PM literature, in the case of improvement of headaches after treating constipation, it can be inferred that the patient may suffer from a secondary headache as a complication of constipation; then, constipation might be considered a new etiology for secondary headaches.

However, more studies are needed to clarify the relationship between headache (non migraine headache especially) and constipation and more studies is needed.

CONCLUSION:

In view of results of the mentioned articles, there is comorbidity between constipation and headache. However, insufficient attention is given to constipation treatment in the process of headache management in

modern medical texts. More than thousand years ago, Persian scholars considered the removal of constipation as the first therapeutic measure in the treatment of headache.

Moreover, the possible implementation of complementary and alternative medicine (CAM) should be taken into account. Since the etiology and detailed treatment of constipation are fully discussed in the context of traditional medicine, we can refer to these guidelines for more effective management of headaches. Overall, we can conclude there is a positive relation between constipation and non-migraine headache (tension headache). However more studies is needed to clarify migraine and constipation.

Presently, considering the high prevalence of constipation in our community, careful attention to this issue can bring more success to management of headache. On the other hand, since constipation is the side effect of some of the medicines used for treating headaches such as calcium channel blockers and tricyclic antidepressants, paying enough attention to choose appropriate medications with no constipation as a side effect might help in more efficient treatment of headache or use of traditional medicine laxatives such as *Golghand* along with the conventional treatment might be suggested.

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Conflict of interest:

The Authors announce that they have no conflict of interes.

REFERENCES:

1. Woldeamanuel YW, Andreou AP, Cowan RP. Prevalence of migraine headache and its weight on neurological burden in Africa: A 43-year systematic review and meta-analysis of community-based studies. *Journal of the neurological sciences*. 2014;342(1):1-15.
2. Society HCCotIH. The international classification of headache disorders, (beta version). *Cephalalgia*. 2013;33(9):629-808.
3. Russell RP. Side effects of calcium channel blockers. *Hypertension*. 1988;11(3 Pt 2):II42.
4. Uher R, Farmer A, Henigsberg N, Rietschel M, Mors O, Maier W et al. Adverse reactions to

antidepressants. *The British Journal of Psychiatry*. 2009;195(3):202-10.

5. Bjarnason I, Hayllar J, Macpherson AJ, Russell A. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology*. 1993;104(6):1832-47.

6. Burris JF. β -Blockers, Dyslipidemia, and Coronary Artery Disease: A Reassessment. *Archives of internal medicine*. 1993;153(18):2085-92.

7. Steiner TJ. Headache in the world: public health and research priorities. 2014:51-7.

8. Organization WH. Atlas of headache disorders and resources in the world 2011. World Health Organisation; 2011.

9. Pal SK, Shukla Y. Herbal medicine: current status and the future. *Asian pacific journal of cancer prevention*. 2003;4(4):281-8.

10. Borhani Haghighi A, Motazedian S, Rezaii R, Mohammadi F, Salarian L, Pourmokhtari M et al. Cutaneous application of menthol 10% solution as an abortive treatment of migraine without aura: a randomised, double-blind, placebo-controlled, crossed-over study. *International journal of clinical practice*. 2010;64(4):451-6.

11. Wang L, Zhang J, Hong Y, Feng Y, Chen M, Wang Y. Phytochemical and pharmacological review of da chuanxiong formula: a famous herb pair composed of chuanxiong rhizoma and gastrodiae rhizoma for headache. *Evidence-Based Complementary and Alternative Medicine*. 2013;2013.

12. Zargaran A, Borhani-Haghighi A, Faridi P, Daneshamouz S, Mohagheghzadeh A. A review on the management of migraine in the Avicenna's Canon of Medicine. *Neurological Sciences*. 2016;37(3):471-8.

13. Motahri M, Fathi M, Nasserri M. The role of the traditional Iranian medicine as a treatment of chronic headache: a case series study. *Iranian Journal of Pharmaceutical Research*. 2010:39-.

14. Choshty, Hakim Mohammad Azam Khan. Azam's Elixir. Tehran. Institute of medicine's history Studies, Islamic and Complementary Medicine, 2008.

15. Aghili-Khorasani. Moalejate Aghili (Aghili's Treatments) (in Persian). Tehran: Research Institute for Islamic and Complimentary Medicine; 2008.

16. Aghili Khorasani, Seyed Mohammad Hussain. "Kholase al Hekma". Correction by professor Nazim. Tehran. First print. Volume 1.

17. Ibn-e-Sina AH. Al-Qanun fit-tib [The Canon of Medicine] (research of ebrahim shamsedine). Beirut, Lebanon: Alaalami Beirut library Press; 2005.

18. M. R. Alhavi fi-al-tibb. Beirut: Dar Ehia Al Tourath Al -Arabi; 2002.

19. Jorjani. Zakhireye Khwarzam Shahi (Treasure of Khwarazm Shah) Tehran: Bonyade Farhange Iran; 1976.

20. Jorjani SI. Al- Aghraz al- Tebbieh va al- Mabahes al-Alayieh [Medical Pursuits. Tehran: Tehran University Press; 2005.
21. Mozaffarpur S, Naseri M, Kamalinejad M, ESMAEILI DM, Yousefi M, Mojahedi M et al. Introduction of natural medicinal materia effective in treatment of constipation in Persian traditional medicine. 2012.
22. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. *BMC gastroenterology*. 2008;8(1):1.
23. Zahedi MJ, Moghadam SD, Abbasi MHB, Mirzaei SMS. The Assessment Prevalence of Functional Constipation and Associated Factors in Adults: A Community-based Study from Kerman, Southeast, Iran (2011-2012). *Govaresh*. 2014;19(2):95-101.
24. Zhao Y, Yu Y-B. Intestinal microbiota and chronic constipation. *SpringerPlus*. 2016;5(1). doi:10.1186/s40064-016-2821-1.
25. Hamedi S, Jokar A, Abbasian A. Viewpoints of Iranian Traditional Medicine (ITM) about Etiology of Constipation. *J Gastroint Dig Syst S*. 2012;8(2):12.
26. Aamodt AH, Stovner LJ, Hagen K, Zwart JA. Comorbidity of headache and gastrointestinal complaints. The Head-HUNT Study. *Cephalalgia*. 2008;28(2):144-51. doi:10.1111/j.1468-2982.2007.01486.
27. Inaloo S, Dehghani SM, Hashemi SM, Heydari M, Heydari ST. Comorbidity of headache and functional constipation in children: A cross-sectional survey. *Turk J Gastroenterol*. 2014;25.
28. Fazljou SMB, Togha M, Ghabili K, Alizadeh M, Keshavarz M. In commemorating one thousandth anniversary of the Avicenna's Canon of Medicine: gastric headache, a forgotten clinical entity from the medieval Persia. *Acta Medica Iranica*. 2013;51(5).
29. Park M-N, Choi M-G, You SJ. The relationship between primary headache and constipation in children and adolescents. *Korean journal of pediatrics*. 2015;58(2):60-3.
30. Spierings EL. Headache of gastrointestinal origin: case studies. *Headache: The Journal of Head and Face Pain*. 2002;42(3):217-9.
31. Noras MR, Kiani MA. Viewpoints of Traditional Iranian Medicine (TIM) about Etiology of Pediatric Constipation. *International Journal of Pediatrics*. 2014;2(1):89-92.
32. Maddahian A, Togha M, Sahranavard S, Riahi S, Dehghan S, Movahhed M. Effect of "Gol-e-ghand", a mixture of rose petals and honey, on migraine attacks: a before-after pilot study. *Research Journal of Pharmacognosy (RJP)*. 2017;4(4):33-9.
33. Arzani, Hakim Mohammad Akbar. "teb e Akbari". Tehran. correction and research by the Institute of Natural Medicine's revival. 2008.
34. Rabner J, Caruso A, Zurakowski D, Lazdowsky L, LeBel A. Autonomic dysfunction in pediatric patients with headache: migraine versus tension-type headache. *Clin Auton Res*. 2016;26(6):455-9. doi:10.1007/s10286-016-0385-3.
35. Le Gal J, Michel J-F, Rinaldi VE, Spiri D, Moretti R, Bettati D et al. Association between functional gastrointestinal disorders and migraine in children and adolescents: a case-control study. *The Lancet Gastroenterology & Hepatology*. 2016;1(2):114-21.
36. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. *SpringerPlus*. 2016;5:637. doi:10.1186/s40064-016-2211-8.
37. Voigt AW, Gould HJ. Chronic Daily Headache: Mechanisms and Principles of Management. *Current Pain and Headache Reports*. 2016;20(2). doi:10.1007/s11916-016-0542-3.
38. Hindiyyeh N, Aurora SK. What the Gut Can Teach Us About Migraine. *Current Pain and Headache Reports*. 2015;19(7). doi:10.1007/s11916-015-0501-4.
39. van Hemert S, Breedveld AC, Rovers JrMP, Vermeiden JPW, Witteman BJM, Smits MG et al. Migraine Associated with Gastrointestinal Disorders: Review of the Literature and Clinical Implications. *Frontiers in Neurology*. 2014;5. doi:10.3389/fneur.2014.00241.
40. Garnock-Jones KP. Prucalopride: A Review in Chronic Idiopathic Constipation. *Drugs*. 2015;76(1):99-110. doi:10.1007/s40265-015-0518-3.
41. Jiang C, Xu Q, Wen X, Sun H. Current developments in pharmacological therapeutics for chronic constipation. *Acta Pharmaceutica Sinica B*. 2015;5(4):300-9. doi:10.1016/j.apsb.2015.05.006.
42. Panczyk K, Golda S, Waszkielewicz A, Zelaszczyk D, Gunia-Krzyzak A, Marona H. Serotonergic system and its role in epilepsy and neuropathic pain treatment: a review based on receptor ligands. *Curr Pharm Des*. 2015;21(13):1723-40.
43. Reuter U, Israel H, Neeb L. The pharmacological profile and clinical prospects of the oral 5-HT1F receptor agonist lasmiditan in the acute treatment of migraine. *Therapeutic Advances in Neurological Disorders*. 2015;8(1):46-54. doi:10.1177/1756285614562419.
44. Forsythe P, Kunze WA. Voices from within: gut microbes and the CNS. *Cellular and molecular life sciences*. 2013;70(1):55-69.