

Chinese Herbal Medicine for Migraine: An Application of Text Mining

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Abstract—Migraine is one of the most chronic disable headache diseases, and it effects 5% to 10% of adults. Patients could not work effectively, or even keep a high quality of life. As a complex neuro-vascular disease, the pathology of migraine is still not fully understood. Many medical methods are applied to release symptoms or prophylaxis of migraine, such as behavior therapy, psychotherapy, acupuncture, massage, and drug therapy. In China, Chinese herbal medicines (CHMs) are also used to treat migraine. Through the long history, and also in modern era, various CHMs are prescribed in different formulae. In clinical practice, a proportion of patients in China will not only take biomedical drugs, but also receive CHMs therapy or combinational treatment. This combination will broaden new field in the management of migraine. To explore some answer to which CHMs are most prescribed in formulae and basic traits of these CHMs, as well as biomedical drugs in combination with these CHMs, we designed a study based on text mining technology for these three questions. In this study, we built a dataset from the information downloaded in Sinomed database. With our novel text mining method, CHMs in this dataset were counted, and some fundamental parameters of each CHM, such as cold/heat property, flavours, and channel tropism were also recorded. Besides, biomedical drugs prescribed together with CHM were also involved in statistic. Results showed that Chuan Xiong, Tian Ma, Dan Shen, Dang Gui and Xi Xin are the top 5 CHMs used to cure migraine. Among all these CHMs, warm CHMs were most frequently used in the treatment of migraine, pungent was the most frequent flavour, and liver, heart are the top 2 channels, both these two viscera were related to human psychoactivity in TCM theory, and further regulate the disease activity of migraine. Cinnarizine, flunarizine, nimodipine, and nitroglycerin were drugs most combined with CHM to cure migraine. These results indicated that text mining could be an effective method in exploring the rules of CHMs prescription and the combination of biomedicine and CHMs in treatment of migraine.

Index Terms—Chinese herbal medicine, text mining, migraine, traditional Chinese medicine

I. INTRODUCTION

Migraine is a common neurological disorder disease affecting about 10% to 20% in population[1]. Different patients may suffer from different symptoms. Its clinical presentation is heterogeneous and may include recurrent headache attacks, associated symptoms of diet disturbance, and hypersensitivity of lots functional systems of the center

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and peri-nervous system[1], [2]. About 1/3 (or one third) migraineurs will further get transient neurological symptoms which mostly related the visual system prior to or during migraine attack, and these are known as migraine aura. Some organizations have set criteria for its diagnosis and treatment, between these organizations, the International Headache Society (IHS) established gold-standard criteria for migraine [3]. Although there comes to common sense that migraine is a neuro-vascular disorder, but the exact pathology of migraine is not still completely understood[4]. Some clinical studies have given evidence of a strong association between migraine, particularly migraine aura, and ischaemic stroke. Late studies focus on the role of migraine as potential risk of endothelial dysfunction[5-9], which may further affect the normal function of vascular endothelial cells. Because endothelial dysfunction always occur in a situation of an increased oxidative stress and pro-inflammatory reaction, this proposed as one of pathogenesis of migraine[10]. Allergic sensitivity are also considered to be one cause of migraine, in theory, allergy offers many suggestive possibilities as an etiological agent in migraine, but further study still need to be done to prove this[11], [12]. And the mechanism between allergy and migraine is not so clear. The importance of psychologic factors in migraine has been well-recognized. Some studies show that an abnormally strong reaction to environmental stress related to migraine. Others also hypothesised migraine patients may have inherited a neurophysiologic system which is undercapable to handle various stresses.

Patients with migraine may suffer strong headache while the symptoms occurs [13], this affects their normal life and work [14]. Normal biofunction of diet order, normal sensitivity of nervous system are also up-regulated for migraine. Besides, migraine patients also in higher risk of cardiovascular disease (CVD), ischemic stroke, psychiatric, neurological, and other pain disorders and even CVD mortality[15]-[17]. So, migraine carries a tremendous individual, societal, and economic burden[18].

In China, migraine is also a major type of headache which suffers Chinese people. Based on traditional Chinese medicine theory, the syndrome patterns of migraine could be classified into different types, such as Liver Yang Rising, Liver Fire Rising, or Phlegm [19]. And several clinical trial have verified that acupuncture and moxibustion could release or control migraine symptoms[19]-[23]. Different syndrome patterns show Chinese herbal medicines (CHM) used to cure migraine are also in certain types. For example, liver could be the most target viscera. While CHM are still the major treatment of Chinese medicine to control migraine, there is growing need to further investigate what types of CHM have been prescribed, and the traits of them.

However, due to the complexity of TCM theory, the treatment rule of migraine are complicated and mysterious. In order to explore the treatment principles more intuitively, a novel text mining method was development based on a comprehensive collection of 6,875 records of literatures[24]. The study would provide an accessible way for exploring the treatment rules for migraine with CHM.

II. MATERIAL AND METHODS

A. Data collection

The dataset are downloaded from SinoMed (<http://sinomed.cintcm.ac.cn/index.jsp>) with the query term of “migraine” on June 22, 2012. This dataset conatins 6,875 records of literatures on clinical practices or theoretical research on migraine, both articles and reviews are on list. In this dataset, each record is tagged with an unique ID. These records contain the title, keywords, and abstract of published papers [18], and these are the resource for data mining.

B. Data analysis

1) CHM used for treating migraine: Chinese herbal medicine: Based on the keyword list of CHMs (both legal names and other popular names are included for calculation), we filtered the CHMs in the plain text format, and then converted all popular names into legal names. All the CHMs are tagged with their unique paper ID. Based on the unique paper ID, we could construct the pairs of co-existed CHMs as they do coexisted in literature. For example, in one paper, CHMs of Huang Qi (Radix Astragali seu Hedysari), Ren Shen (Radix Ginseng), and Sheng Di Huang (Radix Rehmanniae Recens) are mentioned. Then, the pairs of co-existed CHMs of “Huang Qi-Ren Shen”, “Huang Qi-Sheng Di Huang”, and “Ren Shen-Sheng Di Huang” are constructed.

2) Characteristics of CHMs: Based on traditional Chinese medicine thoery, different aspects of characteristics of CHMs, such as four nature (they are cold, heat, warm, and cold), five flavours (they are sour, bitter, sweet, pungent, and salty), ascending and descending, floating and sinking, and channel tropism are listed. These characteristics are recorded from the Chinese Pharmacopeia, 2010 edition. The frequency of charastersics shows what’s in common of these CHMs, and it could also provides clues of principles of CHMs prescription for migraine. Every aspects of characterics are calculated in unweighted number (UWN) and weighted number (WN). The weighting rule is based on the number of CHMs total number in part 1.

3) CHM and western drugs in combination: Besides CHMs, the western drugs which prescided with CHMs are also mined. By combining CHM and western drugs, symptoms of migraine could be more effective controlled. And the most used drug pairs are mined out.

III. RESULTS

In this paper, focused on migraine, we explored principles of CHM used to release the symptoms of migraine and the characteristics of these CHM, as well as the combinations of

biomedical drugs and CHM. Results show that there are some rules for CHM in treating migraine, and considering these rules with the TCM theory of migraine, they logical release the cause of migraine.

- 1) CHM used in treatment of migraine: From 6,875 record of literatures, CHM used for migraine are mined out, and the top 5 are Chuan Xiong, Tian Ma, Dan Shen, Dang Gui and Xi Xin (top 10 CHMs are listed in Fig 1., and the number could also be read).
- 2) Characteristics of CHM: The four nature of herbal drugs, which is considered to be the most inportant characteristics of CHM, shows that warm and plain are the top 2 cold-heat traits (see Fig 2.). The five flavours of herbal medicine show that pungent, bitter, and sweet are the top 3 flavours of herbs for migraine (see Fig 3.). And in channel tropism, liver, heart, spleen, and lung are the most four channels targeted to cure migraine (see Fig. 4).
- 3) CHM and western drugs in combination for migraine: In the research of western drugs and CHM prescribed together, results show that cinnarizine, flunarizine, nimodipine and nitroglycerin are the most simultaneously prescribed western drugs, most of they are Ca²⁺ ion channel antagonist (cinnarizine, flunazine, and nimodipine). Chuan Xiong, Gan Cao, Dang Gui and Qiang Huo are the most simultaneously prescribed CHMs for migraine, and a majority of these CHMs are warm, while minority of them are cool.

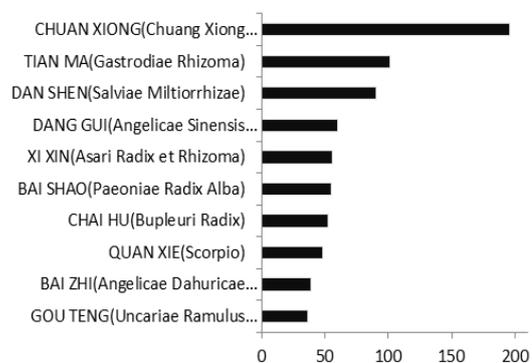


Fig. 1. Top 10 frequently prescribed CHMs in treatment of migraine

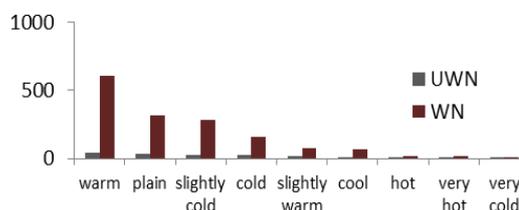


Fig. 2. Numbers of CHM in four nature for migraine (UWN: unweighted number, WN:weighted number)

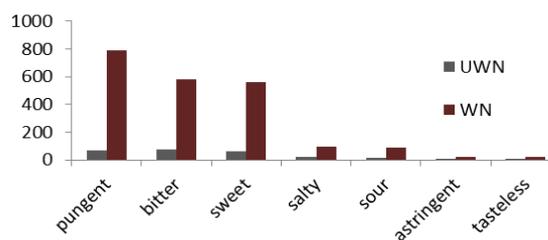


Fig. 3. Numbers of CHM in flavours four migraine (UWN: unweighted number, WN:weighted number)

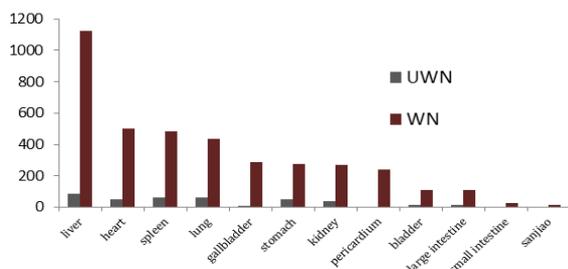


Fig. 4. Numbers of CHM in channel tropism for migraine (UWN: unweighted number, WN: weighted number)

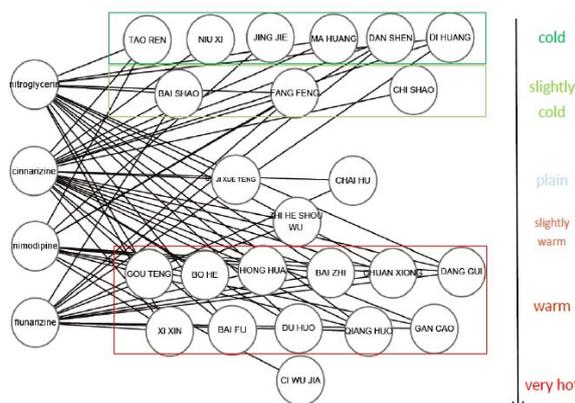


Fig. 5. The most simultaneously prescribed CHMs and Western drugs in treatment of migraine

IV. CONCLUSION AND DISCUSSION

Based on the text mining technology, it is naturally come to a point that Chinese herbal medicines used for treating diseases could also be mined out. Learn from our previous work, a method to mine and summare drugs prescribed in clinical situation of migraine was constructed. From the dataset downloaded from Sinomed, we carried a research on migraine, the answers to these questions were found out: which herbal medicines were used in treating migraine? what are the types of them? which biomedical drugs were prescribed together with them? So, from this study, some simple conclusions could carried out.

- 1) Herbal drugs could be mined out. The drugs used for treating some special disease could be mined out based on text mining technology. Although there are only top 10 medicines listed out in Fig 1., other less used medicines are also figured out. For other clinician, if they are interested in other disease, such as rheumatoid arthritis, or coronary heart diseases, with great application of CHM, this method could also work.
- 2) Parameters of drugs could be figured out. There are rules in prescription of CHM, and most of these rules are learnt from clinical practise or classical book. Both of these two ways are not easy to learn or master. Through text mining, we can easily found out what kinds of CHM are most prescribed in treating migraine, and these simple rules could offer basic clues for treating some disease in TCM theory. Fig 2. to Fig 4. show fundemental parameters of these CHM. Comparing with a rondomized controlled trail in China, herbs for calming liver and suppressing liver-yang in treating migraine showed better outcome[25]. This was

highly consistent with our result, as these herb targeting on liver and suppressing liver-yang, better effect on headache improvement would be observed.

- 3) Drugs combination is also mined out. Not only on CHM, but also on western drugs, could this method be applied. Some most used combinations of CHM and western drugs are mined out. In the situation that more and more physicians prescribe CHM to cure disease or use them with traditional western drugs, this result could be inportant in further research on intergrated drug usage. As we could read in Fig 5., more traditional western drugs in the type of Ca²⁺ ion channel antagonist are in combination with more warm herbal medicines to release symptoms of migraine.

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REFERENCE

- [1] S. R. Haut, M. E. Bigal, and R. B. Lipton, "Chronic disorders with episodic manifestations: focus on epilepsy and migraine," *Lancet neurology*, vol. 5, no. 2, pp. 148-157, 2006.
- [2] S. D. Silberstein, "Migraine," *Lancet*, 2004, vol. 363, no. 9406, pp. 381-391.
- [3] M. Schürks, "Genetics of migraine in the age of genome-wide association studies," *J Headache Pain*, 2012, vol. 13, no. 1, pp. 1-9.
- [4] R. A. Lea, M. Ovcarić, J. Sundholm, J. MacMillan, L. R. Griffiths, "The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura," *BMC Med*, vol. 2, no. 3, 2004.
- [5] D. L. Campo, C. R. Carbajo, M. P. Prieto, S. C. Puerta, E. C. Morollon, and J. Pascual, "Migraine as a vascular risk factor," *Revista de neurologia*, 2012, vol. 55, no. 6, pp. 349-358.
- [6] X. R. Osorio, T. Sobrino, D. Brea, F. Martinez, J. Castillo, R. Leira, "Endothelial progenitor cells: a new key for endothelial dysfunction in migraine," *Neurology*, 2012, vol. 79, no. 5, pp. 474-479.
- [7] T. G. Liman, L. Neeb, J. Rosinski, I. Wellwood, U. Reuter, W. Doehner, P. U. Heuschmann, M. Endres, "Peripheral endothelial function and arterial stiffness in women with migraine with aura: a case-control study," *Cephalalgia*, 2012, vol. 32, no. 6, pp. 459-466.
- [8] D. Perko, J. P. Oblak, M. Sabovic, M. Zaletel, and B. Zvan, "Associations between cerebral and systemic endothelial function in migraine patients: a post-hoc study," *BMC neurology*, 2011, vol. 11, no. 146.
- [9] T. Yonekawa, H. Doi, T. Tateishi, K. Tanaka, T. Iura, Y. Ohyagi, J. Kira, "Migraine with aura and recurrent vertigo attacks in a patient with hereditary hemorrhagic telangiectasia," *Rinsho shinkeigaku = Clinical neurology*, vol. 52, no. 7, pp. 499-502, 2012.
- [10] V. Pizza, A. Agresta, E. Lamaida, N. Lamaida, F. Infante, A. Capasso, "Migraine and Genetic Polymorphisms," *An Overview. Open Neurol J*, 2012, vol. 6, pp. 65-70.
- [11] M. E. Mehle, "Migraine and allergy: a review and clinical update," *Current allergy and asthma reports*, 2012, vol. 12, no. 3, pp. 240-245.
- [12] A. O. Ozen, H. E. Saricoban, N. Mutlu, M. R. Cengizlier, "Relationship between migraine-type headache in childhood with cow's milk allergy and egg-white allergy," *Agri : Agri (Algoloji) Derneği'nin Yayın organidir = The journal of the Turkish Society of Algology*, 2011, vol. 23, no. 4, pp.174-178.
- [13] M. Schürks, P. M. Rist, R. E. Shapiro, T. Kurth, "Migraine and Mortality: A Systematic Review and Meta-Analysis," *Cephalalgia*, 2011, vol. 31, no. 12, pp.1301-1314.
- [14] W. F. Stewart, J. A. Ricci, E. Chee, D. Morganstein, and R. Lipton, "Lost productive time and cost due to common pain conditions in the US workforce," *Journal of the American Medical Association*, vol. 290, no. 18, pp. 2443-2454, 2003.
- [15] P. M. Rist, H. C. Diener, T. Kurth, and M. Schurks, "Migraine aura, and cervical artery dissection: a systematic review and meta-analysis," *Cephalalgia*, 2011, vol. 31, no. 8, pp. 886-896.

- [16] M. Schurks, P. M. Rist, R. E. Shapiro, and T. Kurth, "Migraine and mortality: a systematic review and meta-analysis," *Cephalalgia*, 2011, vol. 31, no. 12, pp. 1301-1314.
- [17] L. S. Gudmundsson A. I. Scher, T. Aspelund, J. H. Eliasson, M. Johannsson, G. Thorgeirsson, L. Launer, and V. Gudnason, "Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study," *BMJ*, 2010, vol. 341, no. 3966.
- [18] L. Stovner, K. Hagen, R. Jensen, Z. Katsarava, R. Lipton, A. Scher, T. Steiner, J. A. Zwart, "The global burden of headache: a documentation of headache prevalence and disability worldwide," *Cephalalgia*, 2007, vol. 27, no. 3, pp. 193-210.
- [19] G. Bowing, J. Zhou, H. G. Endres, R. R. Coeytaux, H. C. Diener, A. F. Molsberger, "Differences in Chinese diagnoses for migraine and tension-type headache: an analysis of the German acupuncture trials (GERAC) for headache," *Cephalalgia*, 2010, vol. 30, no. 2, pp. 224-232.
- [20] J. A. Andrade, J. A. M. Junior, X. Carne, V. Severino, G. M. asconcelos, and H. R. C. Filho, "Acupuncture in migraine prevention: a randomized sham controlled study with 6-months posttreatment follow-up," *The Clinical journal of pain*, vol. 24, no. 2, pp. 98-105, 2008.
- [21] G. Allais, S. Rolando, I. C. Gabellari, C. Burzio, G. Airola, P. Borgogno, P. Schiapparelli, R. Allais, and C. Benedetto, "Acupressure in the control of migraine-associated nausea," *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, 2012, vol. 33, pp. 207-210.
- [22] P. Chen, "Observation on therapeutic effect of migraine treated with medicated threads moxibustion of Zhuang nationality," *Zhongguo zhen jiu = Chinese acupuncture and moxibustion*, vol. 32, no. 3, pp. 224-226, 2012.
- [23] H. C. Diener, K. Kronfeld, G. Boewing, M. Lungenhausen, C. Maier, A. Molsberger, M. Tegenthoff, H. J. Trampisch, M. Zenz, R. Meinert, "Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial," *Lancet neurology* 2006, vol. 5, no. 4, pp. 310-316.
- [24] G. Zheng, M. Jiang, X. He, J. Zhao, H. Guo, G. Chen, Q. Zha, and A. Lu, "Discrete derivative: a data slicing algorithm for exploration of sharing biological networks between rheumatoid arthritis and coronary heart disease," *BioData mining*, vol. 4, no. 18, 2011.
- [25] G. W. Zhong, W. Li, Y. H. Luo, G. L. Chen, Z. J. Yi, J. J. Hu, Y. Zhang, Y. H. Yin, L. Zhang, "Herbs for calming liver and suppressing liver-yang in treatment of migraine with hyperactive liver-yang syndrome and its effects on lymphocyte protein expression: a randomized controlled trial," *Zhong xi yi jie he xue bao = Journal of Chinese integrative medicine*, vol. 7, no. 1, pp. 25-33, 2009