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Wen Dan Tang: A Potential Jing Fang Decoction for Headache Disorders

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Keywords:

Chinese Herbal Medicine; Wen Dan Tang; Traditional Chinese Medicine; Headache Disorders; Migraine; Tension-Type Headache

1. Abstract

1.1 Background: Chinese herbal medicine is considered relatively safe, inexpensive, and easily accessible. Furthermore, it is becoming increasingly popular in the western countries.

Wen Dan Tang, a Jing Fang ancient classical Chinese herbal formula, with a broad indication profile, has been used for several centuries in China to treat various illnesses.

1.2. Question: Are there evidence-based clinical trials, which show that Wen Dan Tang has a significant impact on the treatment of various diseases, especially in patients with migraine and tension-type headache?

1.3. Methods: This study is based on an online database search using PubMed, Medline, Cochrane Library, AcuTrials, Embase, Semantic Scholar, Jstor, internet research and review of ancient and modern Chinese medical textbooks regarding Wen Dan Tang and its compounds.

1.4. Results: There were no studies on Wen Dan Tang in migraine and tension-type headache, therefore this work gathers and describes data for each single compound in the formula.

1.5. Conclusion: This study suggests that the bioactive compounds found in Wen Dan Tang and Wen Dan Tang composition shows potential in the treatment of patients with neurological, psychiatric disorders, cardiovascular diseases, metabolic syndrome, and digestive disorders. Some coherence between Wen Dan Tang in headache reduction and the improvement of the quality of life in migraine and tension-type headache patients could be evaluated, showing positive results of Wen Dan Tang for these patients.

2. Introduction

The implementation of Traditional Chinese Medicine (TCM) still carries on since thousands of years predominantly in China and generally in Asia, for prevention and treatment of numerous medical conditions.

Wen Dan Tang (WDT) also known as “Warm the Gallbladder decoction” is a classical famous Chinese herbal formula containing eight components:

Pinellia ternata (Thunb.) Makino (Ban Xia), Bambusa tuldoides Munro (Zhu Ru), Citrus aurantium L. (Zhi Shi), Citrus reticulata Blanco (Chen Pi), Glycyrrhiza uralensis Fisch (Gan Cao), Poriae sclerotium cocos albae (Fu Ling), Zingiber officinale Roscoe (Gan Jiang), and, Ziziphus jujuba Mil (Da Zao) (Table 1) [1, 2].

Table 1: WDT origins and functions listed in table 1.

Species	Function	Reference
Pinelliae Rhizoma (Pinellia ternata (Thunb.)1 Makino)	Ceases cough, dissolves phlegm, dries dampness, stops vomiting and possesses anti-tumor effects	(207)
Caulis Bambusae In *Taenia* sp. (Bambusa tuldoides Munro)1	Arrests vomiting, alleviates fever, abdominal pain, diarrhea, chest diaphragm inflammation, antifatigue attribute, regulates hypertension and hyperlipidemia, reduces aggravation	(208,209)
Fructus Aurantii Immaturus (Citrus aurantium L.)1	Gastrointestinal disorders, anti-coagulation, eliminates food stagnation by guiding the Qi downwards, anti-anxiety properties	(210,211)
Citri reticulate Pericarpium (Citrus reticulata Blanco)1	Dissolves phlegm, dries dampness, promotes Qi, and strengthens spleen, anti-asthmatic characteristic.	(212–214)
Glycyrrhizae Radix et Rhizoma (Glycyrrhiza uralensis Fisch)1	Tonifies Qi and the spleen, harmonizes the action of all herbs in a prescription and eliminates the toxicity of herbs.	(215,216)
Poria Cocos (Poriae sclerotium cocos albae)1	Strengthens the spleen and harmonizes the stomach, anti-anxiety properties, calmative, soothing diuretic effect.	(217,218)
Zingiberis Rhizoma(Zingiber officinale Roscoe)1	Antiemetic effect, alleviates pain, harmonizes the stomach and spleen, warms the centre and the lungs, removes cold	(219,220)
Jujubae Fructus (Ziziphus jujuba Mil)1	Nurtures the blood, calmative effect, promotes Qi, tonifies the stomach and spleen, regulates digestive system, reduces the toxicity of herbs.	(221,222)

[1] The accepted Nomenclatural name of the species validated by www.theplantlist.org

Classically WDT is a TCM prescription for disorders of the spirit and has been used for 100 of years to treat symptoms like schizophrenia. Deng and Xu have shown that WDT may have some positive short-term antipsychotic effects compared to placebo or no treatment. Nevertheless, combining WDT with an antipsychotic reduced the adverse effects of antipsychotics. [3]. Clinically WDT is used to treat psychiatric disorders (such as schizophrenia, major depressive disorder, and anxiety), insomnia, stroke, digestive disorder, metabolic syndrome, and cardiovascular disease [3, 13]. Additionally, WDT is considered relatively safe, economical and obtainable [3].

Sun Si Mao (580-682 A.D.), who was honored as the "King of Herbal Medicine", completed a 30-volume encyclopedia entitled Prescriptions Worth a Thousand Pieces of Gold for Emergencies including 4500 Chinese herbal formulae and a treatise on medical practice [14]. He describes in the mentioned encyclopedia, among others the components, properties, function and preparation of WDT [15]. The classification method of disease disorders in this compendium derives from the Yellow Emperor's Inner Canon, Treatise on Cold Pathogenic and Miscellaneous Diseases and General Treatise on Causes and Manifestations of All Diseases [16].

In 2018, Sun Si Mao's WDT was listed in the Catalogue of Ancient Classics Formulae (ACF) among the other 99 ACF's by the National Administration of Traditional Chinese Medicine [1].

WDT is available as a classical Chinese decoction, granules, pills, or hydrophilic concentrate. This hydrophilic concentrate from the Dr. Noyer AG/TCM pharmacy in Switzerland is produced according to the Kumagawa method. Each substance is preserved for one night in purified water and then extracted with the so-called Kumagawa-Extractor. During this process, the substances are dissolved like in a decoction process. At the end of the procedure glycerin is added to ensure durability of the hydrophilic concentrate. Only boiled water as solvent is used in the Kumagawa-Extractor. The extract obtained is therefore very similar to decoction but contains more API agents. This means that smaller quantities can be administered for an identical result compared to decoction [17].

Headache disorders (HD) affect all ages, gender and have become a widespread public health burden [18]. Headache not only influences the individuals' constricted quality of life (QoL) and health but also entails enormous economic costs [19].

The present valid «International Classification of Headache Disorders» (ICHD-3) published in 2018 [20] distinguishes between primary and secondary headaches, as well as neuropathies and facial pain, with more than 300 different types of headache, presented in a hierarchical structure for diagnosis. The most prevalent HD is migraine and Tension-Type Headache (TTH).

According to TCM, a person is healthy when Yin and Yang, vital energy (Qi) and blood in the body, are in balance and the Qi can flow freely in the conduit pathways. All complaints arise by disorders aroused by blockages of qi and/or blood or lack of qi and/or blood and when Yin and Yang in the body become unbalanced [21].

Endogenous factors for headaches from the point of TCM's view are mostly hyperactivity of liver yang, deficiency of qi and blood, spleen, kidney weakness and ascending stagnated fire to the brain [22].

The western medicine pharmacotherapy treatment for HD includes acute and preventive medications [23]. In comparison to western medicine the treatment with WDT can hypothetically be applied for all types of HD.

Additionally, there have been numerous research showing WDT usage in the treatment of various diseases that might lead to HD [3, 13].

Thus, WDT might be beneficial in prophylactic treatment as well. From our clinical experience over years, a very large number of patients reported an improvement of their HD and their QoL after WDT intake. Therefore, it was our approach to review the litera-

ture regarding the application of WDT in migraine and TTH.

2.1. Question: Are there evidence-based clinical trials, which show that WDT has a significant impact on the treatment of HD, especially migraine and TTH?

3. Methods

3.1. Search Strategy

Research data were acquired from PubMed, Medline, Cochrane Library, AcuTrials, Embase, Semantic Scholar, Jstor, internet and additionally ancient and modern Chinese medical textbooks regarding WDT were reviewed, then studies based on our aim were selected.

Search terms were as following: headache disorders, Wen Dan Tang, Wen Dan Tang pharmacological reaction, migraine, tension type headache, Wen Dan Decoction, WDT mechanisms of action.

3.2. Inclusion criteria

Inclusion criteria contained reviews and peer-reviewed research articles exploring the effects of WDT.

3.3. Results

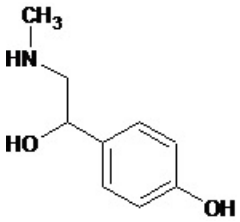
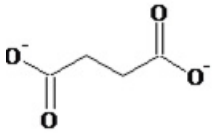
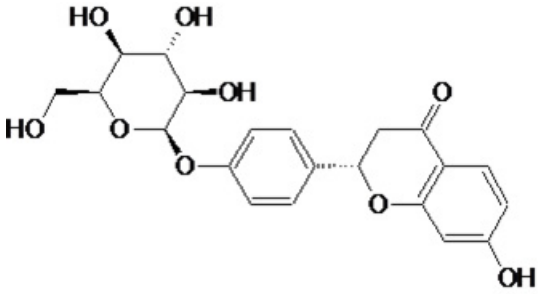
Systematic reviews and peer-reviewed research articles were evaluated for this study.The results were analyzed, classified and summarized. There were no studies on WDT in migraine and TTH, therefore results and studies for the single compounds are described instead.

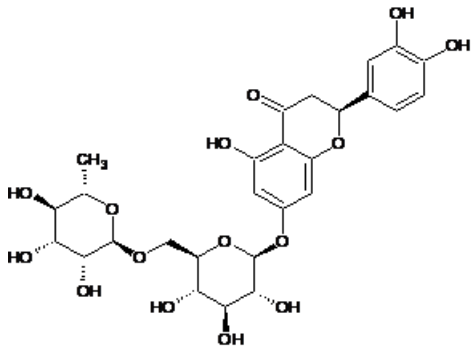
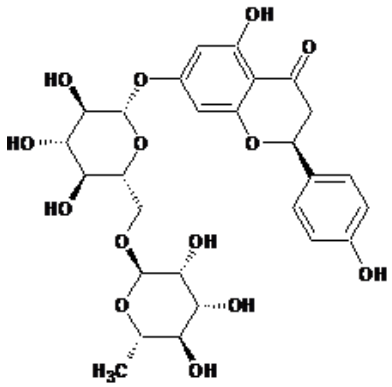
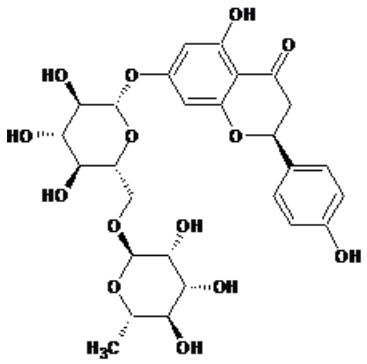
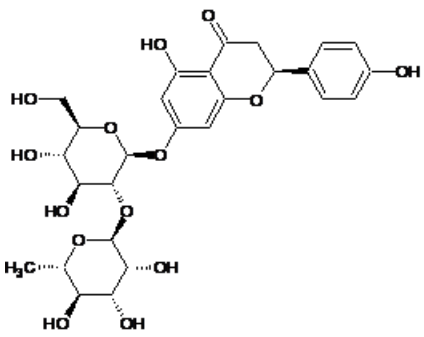
4. Discussion

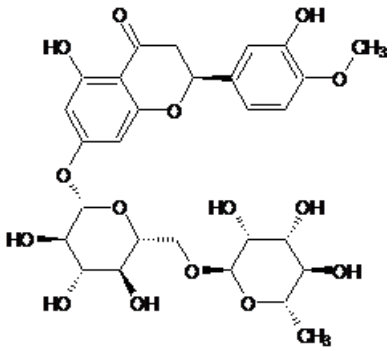
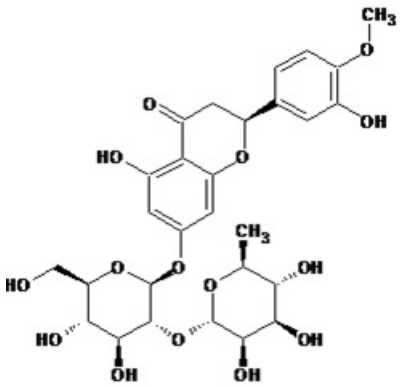
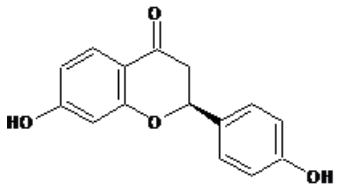
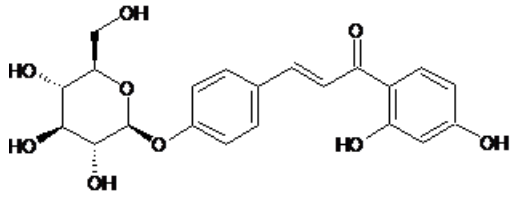
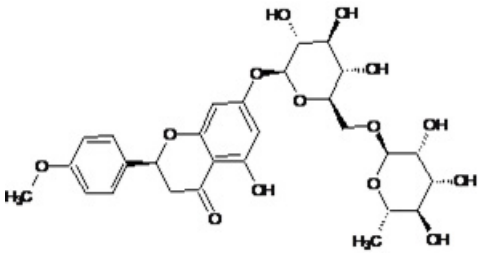
In ancient China, WDT was applied to arouse the courage in a person. According to TCM WDT function is to remove heat-phlegm and harmonize the gallbladder and the stomach. The effects of WDT are sedative, anxiolytic, anti-depressive, regulating the flow of vital energy (qi), expectorant, heat eliminating, harmonizing the stomach and encouraging [24, 25]. As Gallbladder is the source of courage in TCM, the phlegm heat may cause anxiety, restlessness, insomnia, and agitation. The flow of the rebellious Qi in stomach may cause stomach upset. WDT clears phlegm and heat, regulates Qi, harmonizes the gallbladder and the stomach, and calms the Spirit [26].

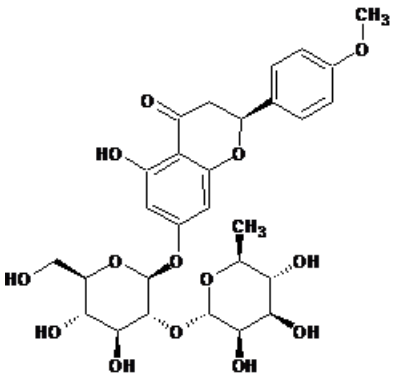
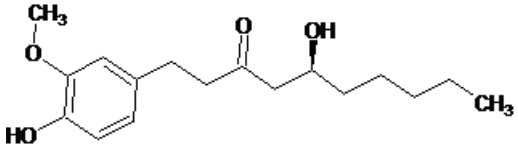
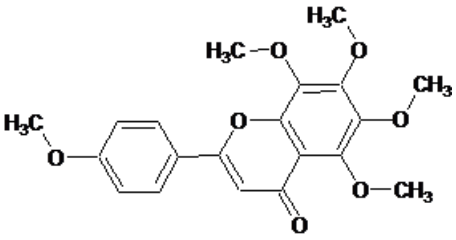
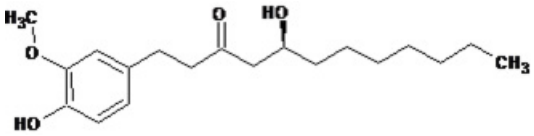
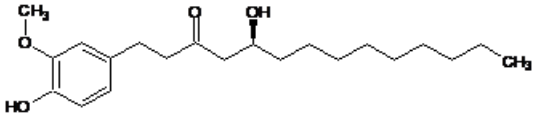
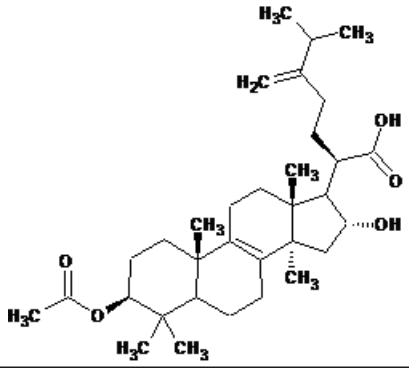
Modern scientific research provided with the evidence that WDT contains compounds including flavonoids, phenols, alkaloids, triterpenoids organic acid, polysaccharides and phosphodiesterase inhibitors (Table 2), which have been found to possess neuroprotective, neuromodulation, anti-mutagenic, antioxidant, antiemetic, antithrombotic, antipyretic and anti-inflammatory effects [2, 27-34].

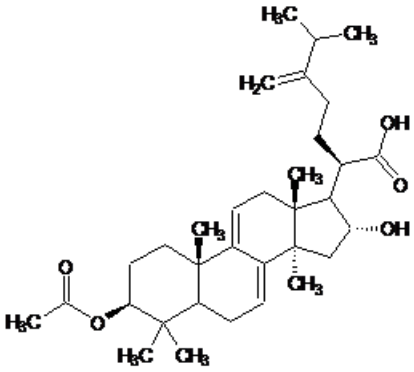
Table 2: A list of bioactive compounds contained in WDT, as defined by Zhang et al. is listed in table 2. (2)

No.	Compound	PubChem CID[1]	Chemical Structure[1]
1	Synephrine		
2	Succinate	160419	
3	Liquiritin	503737	

4	Eriocitrin	83489	
5	Rutin	5280805	
6	Narirutin	442431	
7	Naringin	442428	

8	Hesperidin	10621	
9	Neohesperidin	442439	
10	Liquiritigenin	114829	
11	Isoliquiritin	5318591	
12	Didymin	16760075	

13	Poncirin	442456	
14	6-Gingerol	442793	
15	Tangeretin	68077	
16	8-Gingerol	168114	
17	10-Gingerol	168115	
18	Pachymic acid	5484385	

19	Dehydropachymic acid	15226717	

[1] All Chemical structures were redrawn with (ACD/ChemSketch Freeware) (223) after being retrieved from National Centre for Biotechnology Information (2020). PubChem Compound Summary for CID number above. Retrieved September 25, 2020 from https://pubchem.ncbi.nlm.nih.gov/compound.

Table 3: Application of WDT in various syndromes listed in table 3.

Author (Reference)	Title	Syndrome
●(10)	●Treatment of Insomnia with Traditional Chinese Herbal Medicine.	Insomnia
●(11)	●Wendan decoction for primary insomnia.	
●(29)	●Wen-Dan Decoction Improves Negative Emotions in Sleep-Deprived Rats by Regulating Orexin-A and Leptin Expression.	
●(8)	●Consistent Efficacy of Wendan Decoction for the Treatment of Digestive Reflux Disorders.	Digestive disorder
●(224)	● Wendan decoction for dyslipidemia: Protocol for a systematic review and meta-analysis	Metabolic syndrome
●(9)	●Metabolomic investigation into molecular mechanisms of a clinical herb prescription against metabolic syndrome by a systematic approach.	
●(7)	●Efficacy of the wen dan decoction, a Chinese herbal formula, for metabolic syndrome.	Psychiatric disorders
●(6).	●Behavioural screening of zebrafish using neuroactive traditional Chinese medicine prescriptions and biological targets.	Major depressive disorder
●(3)	●Wendan decoction (Traditional Chinese medicine) for schizophrenia	Schizophrenia
●(5)	●Effects of Wen Dan Tang on insomnia-related anxiety and levels of the brain-gut peptide Ghrelin.	Anxiety
●(225)	●Wen Dan Decoction for hemorrhagic stroke and ischemic stroke.	Stroke
●(12)	●Systems Pharmacology Dissection of Traditional Chinese Medicine Wen-Dan Decoction for Treatment of Cardiovascular Diseases.	Cardiovascular Diseases

5. Alkaloids

Alkaloids are biologically active, organic, nitrogen-containing compounds that widely occur in various plant families such as the nightshade-, poppy- and buttercup family [35]. The nitrogen atom/s of true alkaloids is usually within a heterocyclic ring and derives from an amino acid. They are often optically active, mostly left-handed, and in pure form normally colorless crystalline substances [36].

The bioactive alkaloid within WDT is synephrine [2, 29], which is a phenylethylamine derivative [37], also found in the bitter orange (Citrus aurantium L. from the Rutaceae family) [38]. There are three isomeric forms of synephrine: m-synephrine, p-synephrine and o-synephrine. P-synephrine, stimulating an alpha-1 and beta-3 adrenoreceptors [39]. It causes a stimulation through its direct binding to the alpha-adrenoreceptor, which leads to a contraction of the smooth muscles, thus causing a vasoconstriction of the blood vessels, e.g. in the mucous membranes [40]. The rhinitis induced secondary headache can for instance be reduced by the bioactive substance synephrine [41].

Synephrine belongs to the trace amines synthesized from aromatic amino acids in mammals [42]. An increased level of plasma trace amines was shown to occur in both cluster headache and migraine patients. The alteration in biogenic amine metabolism is one of the characteristics in primary headache sufferers [43]. Additionally, dopamine and trace amines abnormal levels may contribute to the metabolic cascades that predispose headaches occurrence [44].

Migraine is a neurovascular disorder related with impairment of the cerebral nerves and blood vessels. Calcitonin Gene-Related Peptide (CGRP) is the most effective peptidergic vasodilator of peripheral and cerebral blood vessels. CGRP is unleashed to sensory nerves during severe migraine outbreak and has for long time been considered to play a very important role in the pathophysiology of migraine. Farooqui T. has reported a hypothetical molecular mechanism underlying cluster and/or migraine headaches. One of the most accepted mechanism indicates that the release of CGRP results in vasodilation and cranial meningeal stimulation, causing primary headache [45]. As synephrine has been described to exert vasoconstrictive effects, it can be assumed that consumption of

synephrine could contribute to the reduction of the so caused primary headaches.

The beta-3-adrenoreceptors are located in white and brown adipocytes [46] and play an important role in lipolysis and thermogenesis [40]. Synephrine activates the beta-adrenoreceptor and elevates cyclic AMP (cAMP) levels due to the adenylyl cyclase activation. The rise in cAMP levels, which might lead to migraine [47], leads to a surge release of fatty acids from the adipose tissue and consequently promotes fat oxidation by increasing the thermogenesis [48]. In a study published in the British Journal of Clinical Pharmacology by Gutiérrez-Hellín et al., p-synephrine showed a significant increase in fat burning at low-to moderate exercise intensity without changes in heart rate or blood pressure [49–51].

P-synephrine is chemically like ephedrine, but in contrast to synephrine, ephedrine exhibits bindings to beta-1, beta-2 and beta-3 receptors leading to more adverse effects such as hypertension, tachycardic arrhythmias, hyperthyroidism, and an increase in respiratory rate [52]. Consequently, p-synephrine can't be categorized as a stimulant [53, 54].

P-synephrine consumption at recommended levels has been shown to be safe [38]. The low toxicity of p-synephrine and Citrus aurantium L. extracts in mice tested in an in vitro model at high dose was shown by Arbo et al. and Rossato et al. to cause low or insignificant cardiotoxicity [55–58].

In a randomized controlled trial, Bond et al. compared the effect on headache frequency in women with comorbid migraine and overweight/obesity and came to the conclusion that weight loss will improve the QoL of the affected person and might be promising in reducing migraine headaches frequency [59].

Kaats et al. could provide evidence in a randomized double-blinded placebo-controlled study that a chocolate-flavored chew with bitter orange extract containing p-synephrine could significantly suppress appetite, increased energy, and decreases in food intake without adverse effects [60].

Depression and anxiety are very often seen as comorbidity in HD patients [61–64]. Kim et al. outlined the antidepressant-like activity in p-synephrine [65] and the effects of Citrus aurantium L. essential oil regarding the treatment of anxiety and depression has been discussed in several studies [66–71]. Citrus aurantium L. is an essential oil with a potential benefit for pain reduction and the QoL improvement for HD patients.

6. Phenols

Phenol is a hydroxybenzene, which is an aromatic organic compound. In pure form it is colourless-to white crystalline [72].

The substances contained in WDT are gingerols [2, 29], a group of volatile phenolic compounds [73, 74]. Gingerols are categorized according to their alkyl chain length e.g. [6]-gingerol, [8]-gingerol, [10]-gingerol, whereas [6]-gingerol is the most abundant compound segregated from ginger, while other gingerols are present in lower concentrations [74, 75]. Chemically, gingerols are methoxy-substituted phenols with an alkyl side-chain that carries one keto and one hydroxy group each [76].

Gingerols are known to have beneficial medicinal properties and exert remarkable pharmacological and physiological activities. Several pre-clinical studies have supported their role in the treatment of several disorders like diabetes, pain, fever and inflammation [74, 77].

A current hypothesis is that oxidative stress plays a major role in migraine pathogenesis [78–80]. Studies have demonstrated that gingerols possess a high antioxidant effect by inhibiting superoxide and nitric oxide production and suppressing lipid peroxidation [74, 77, 81–87]. It can be assumed that the established anti-oxidative activity of gingerols and specifically of [6]-gingerol might be advantageous for the treatment of HD [31, 74, 88].

A connection between prostaglandin and migraine-like attacks has already been shown (89,90). Gingerols have a function as a suppressor of pro-inflammatory cytokines, inhibiting prostaglandin and leukotriene biosynthesis [91–93], and might therefore be suitable antipyretic for prostaglandin-induced HD treatment [31, 94].

Studies in human liver cell lines indicate that [6]-gingerol decreases inflammation and oxidative stress by decreasing mRNA levels of inflammatory factor interleukin 6 (IL-6), interleukin 8 and serum amyloid A1(95). In vivo models with treatment and topical application of [6]-gingerol to mice exhibited anti-inflammatory activity as well [96, 97]. The reduction of inflammatory factors was shown to be antidepressant effect in animal model of depression [98, 99]. Furthermore, gingerols play an important role influencing the absorption of glucose by increasing cell surface distribution of the glucose transporter Type 4 (GLUT-4) protein [100, 101], a glucose transporter which regulates the insulin-dependent glucose uptake in skeletal muscles [102, 103]. Insulin attaches to the alpha-subunit of the insulin receptor and thus ensures an increase in phosphoinositide 3-kinase (PI3K. The signal transmission at the GLUT-4 caused by PI3K binding to the cell membrane resulting in an increase in the transport of glucose into the muscle cells [104, 105].

A typical adverse effect of a hypoglycemic state is headache. The ICHD-3 classifies this HD as a headache attributed to other metabolic or system disorder ICHD-3 A10.8.2 (20). Hypoglycemic state can be prevented by the increased absorption of glucose [106].

Many HD patients suffer from nausea and emesis before or during their migraine attacks [107, 108]. Studies showed that gingerol could suppress emetic signal transmission in vagal afferent neurons by inhibiting the 5-hydroxytryptamine 3 as well as being antagonistic to acetylcholine receptors [109–115]. The efficacy of ginger compounds on the prevention of nausea and vomiting of

various origins, albeit with the limits of the chemical stability of the gingerol compounds was highlighted in a systematic review of randomized controlled trials [116]. Moreover, gingerols have been shown to selectively inhibit the inducible form of cyclooxygenase-2 (COX-2), but not the constitutive form cyclooxygenase-1 (COX-1). As inhibition of COX-1 is associated with gastrointestinal side effects, selective inhibition of COX-2 might help minimization of these side effects [117]. Hence using ginger to reduce nausea and emesis in HD patients would be suggestive approach.

Gingerols have been shown to have further bioactive effects such as being cardiotonic, antiemetic, anti-inflammatory, anti-tumor-promoting, anti-platelet aggregation in migraine [118], antifungal, analgesic and antibacterial [106, 119–124]. According to Zick et al., healthy humans can tolerate [6]-, [8]- and [10]-gingerols till 2000 mg [125].

7. Isoflavonoids

Isoflavonoids are plant secondary metabolites and a subclass of flavonoids [126]. They are defined by a B-ring attached at the C-3 position of their C-ring and are derived from the flavonoid biosynthesis pathway via liquiritigenin or naringenin [127]. The Isoflavonoid group includes isoflavans, isoflavononones, isoflavones, rotenoids coumestans and pterocarpans. Isoflavonoid compounds have biological effects via the estrogen receptor. They are natural selective estrogen receptor modulators, have a structural similarity to 17-β-estradiol [128], bind especially to the β-estrogen receptor in the brain, have osteo-protective effects and alleviate menopausal symptoms [129]. Migraine attacks are intensified due to increased estrogen levels in women [130]. WDT contains isoflavones [2, 29] which could improve migraine caused by elevated estrogen level and/or prevent menstrual associated migraine [131, 132].

Besides several flavonoids, WDT also contains isoflavonoids such as liquiritin and liquiritingenin [2, 29]. Liquiritin is the 4'-O-glucoside of flavanone liquirtingenin [133]. Liquiritin and Liquirtingenin are characterized by their antioxidant, anti-inflammatory, anti-rheumatoidal and neuroprotective effects [134–136].

8. Liquiritin, Liquiritingenin and Isoliquiritigenin

Radix Glycyrrhizae (RG) is the rhizome of Glycyrrhiza ruralness Fisch., Glycyrrhiza inflate Bat. or Glycyrrhiza glabra L. from the Leguminosae/Fabaceae, which are widely distributed in the northeast and northwest of China. The dried roots and rhizomes (GU), commonly known as licorice in Pharmacopeias [137, 138], is one constituent of WD. Licorice was shown to have antitussive, expectorant, and antipyretic effects, and mostly used for its therapeutic effects alleviating cough, pharyngitis, bronchitis, and bronchial asthma [133, 139, 140].

The sweet-tasting bioactive saponin (Glycyrrhizin) is present in all Glycyrrhiza species. Glycyrrhizin can provoke hypertension, sodium salt and water retention, and potassium ion levels reduction [141, 142]. Higher doses of glycyrrhizic acid (400 mg/day) have risky side effects including cardiac dysfunction, edema, and hypertension [143]. Nevertheless, the medicinal plants have beneficial chemical constituents, Liquiritin (LT), Liquiritingenin (LTG) and Isoliquiritigenin (ISL), that produce physiological changes of various health benefits [133, 144]. There are at least 400 different chemical compounds in RG along with triterpenoid saponins, flavanones, chalcones, coumarins, and their glycosides [133, 140, 145, 146].

The main bioactive flavonoid compounds in RG, LTG and ISL, were identified and isolated from the crude extract of Glycyrrhiza uralensis [147, 148]. ISL demonstrates antioxidant, anti-inflammatory, anti-tumor and hepatoprotective activities. Additionally, LTG is an estrogenic compound which acts as a selective agonist for the β-subtype estrogen receptor [133]. Moreover, derivatives of ISL and LTG were shown to have in vivo anti-diabetic activity [149].

LTG pretreatment significantly reduced the LPS-induced depression symptoms in animal model with decrease in the levels of the pro-inflammatory cytokines in serum and hippocampus compared with the control LPS group (150). LTG have shown to lower the expression of brain-derived neurotrophic factor (BDNF), and p-TrkB (tropomyosin receptor kinase B) [151], indicating that the antidepressant and antianxiety activities of LG/LTG might be due to anti-inflammatory and BDNF/TrkB pathways [150]. In the hippocampus of animal model of depression, LG upregulated the concentrations of 5-hydroxytryptamine (serotonin; 5-HT) and norepinephrine (NE) and acting on the PI3K/Akt/mTOR–mediated BDNF/TrkB pathway in the hippocampus [133, 151].

These facts suggest that LTG could ease depressive-like symptoms in mice model of depression (151). Additionally, other reports indicated that LTG and ISL might act as major MAO inhibitors which in turn beneficial in the treatment of anxiety and depression and consequently as preventive measure for HD [151–153].

In addition, ISL and LTG showed effective prevention of glutamate-induced toxicity by attenuation of mitochondrial malfunction and thus might help to inhibit neurodegeneration [154, 155] and related HD symptoms. However, LTG showed no effect on capsaicin-induced activation of the transient receptor potential vanilloid-related (TRPV1 receptors). It inhibited concentration dependently allyl isothiocyanate (AITC)-induced TRPA1 receptors activation. Additionally, LG treatment in HEK293 cells altered TRPM7-dependent inward/outward currents without alteration in cell proliferation and viability. Thus, hinting its TRP channel-inhibiting properties may be of potential in the development of novel and tolerable analgesic therapies [156].

Glycyrrhizic acid (GA) and 18β-glycyrrhetinic acid (18βGA) are active metabolites of GU extract that mimic aldosterone action in Human physiology. They specifically inhibit the 11β-hydrox-

ysteroid dehydrogenase type 2 (11β-HSD2) enzyme and therefor stop the conversion process of cortisol to cortisone prolonging its half-life and increase cortisol activities level [157]. Thus, might lead to increased vasoconstriction of brain blood vessel which counteract vasodilation induced HD.

Studies have shown ISL could inhibit inflammation for parameters such as interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α), a signaling substance secreted by macrophages during inflammation [158–161]. Although the etiology of migraine isn't fully understood, there is some evidence of increased levels of IL-1β and TNF-α in migraine and chronic Tension-Type Headache (TTH) [162–164]. The implementation of WDT containing isoflavonoid compounds might be suitable for patients in the treatment of HD.

Liquiritin has been shown to inhibit progesterone metabolism by competitively inhibiting Aldo-keto reductase family 1 member C1, an enzyme transforming progesterone to an inactive form and thus limiting the biological effect of progesterone (165). Considerable evidence allows a link between estrogen and progesterone and migraine [166–169]. Migraine appears more intermittently in adult women comparable in men (168, 170). Menstrual-related migraine occurs generally at the time of menses in many migranous women, and exclusively with menses in some [171]. Menstrual related migraine is often associated with other menstrual symptoms such as nausea, breast tenderness and cramps. All symptoms appear to be the result of falling estrogen and progesterone levels [172]. As LG-induced inhibition of progesterone metabolism contributes to stability of progesterone concentration levels, liquiritin might have a positive effect against migraine, nausea and other menstrual-related symptoms.

Chen et al. have described liquiritin's antidepressant effects through fibroblast growth factor-2 enhancement by inhibiting neuroinflammation and maintaining synaptogenesis [173]. Treatment of mice with LTG followed by polysaccharides injection, which causes acute depressive behavior, has led to decrease of pro-inflammatory cytokines IL-6 and TNF-α in serum and hippocampus, when compared with the control [150]. These antidepressant and antianxiety activities of LTG can contribute to improved patients' life quality.

9. Triterpenes

Triterpenes are natural compounds derived biosynthetically from isoprene, consist of six isoprene units and 30-carbon atoms (174). The vast majority of triterpenes are composed of tetra- or pentacyclic compounds [175]. Triterpenes form the basic structure of many saponins, tetrapenes and steroids. They can be divided into three classes according to polarity: liphophilic triterpenes, highly oxidized triterpenes and hydrophilic, glycosidic triterpenes (176).

Pachymic acid, a representative of the triterpenes, is contained in WDT as a bioactive component (2) which is found in the fungus Poriae sclerotium cocos albae (PC), a family of polyporaceae. It is claimed to have many pharmacological effects such as anti-inflammatory, antioxidant, anti-emetic, diuretic and anti-tumor (177–179).

Pachymic acid exerts an insulin-like, hypoglycemic activity by inducing glucose transporter type 4 gene expression and translocation to the plasma membrane in mammalian 3T3-L1 adipocytes, resulting in increased glucose uptake activity (180). As headache prevalence is greater in patients with diabetes than in non-diabetic patients (181).

Clinically PC is mostly implemented in the treatment of hepatitis B, diabetes, cancer, metabolic syndrome and in the modulation of the immune system (182, 183).

10. Organic Acids

Organic acids are organic compounds with a carboxylic group as a functional group. They release hydrogen ions or hydronium ions in water and have the function to donate a proton (184).

WDT contains succinate as a bioactive compound (2). Succinate, an important metabolite, is an esterification of succinic acid and interacts in various processes in the cell (185).

The most common, curable nutrition disorder is iron deficiency. Iron Deficiency Anemia (IDA) in adults, mostly women, in industrialized countries has a prevalence of up to 5% (186, 187). Main symptoms of IDA are fatigue, vertigo, insomnia, depression, headache, brittle nails etc. Serotonin, a neurotransmitter, widely found in the central and peripheral nervous systems, plays a crucial role in migraine neurobiology (188). An increase of 5-hydroxyindoleacetic acid in the urine during a migraine attack could be observed by Gasparini et al. for the first time (189). In migraine attacks the level of serotonin is decreased in the central nervous system, but increased in the peripheral nervous system (189). As iron plays a primary role in the synthesis of serotonin, dopamine and norepinephrine, IDA could be responsible for a reduced level in serotonin (190).

Studies have shown coherence between IDA, hemoglobin and serum ferritin levels and the headache and or migraine occurrence, mainly in women (191, 192). There are several effective methods in the treatment of IDA. Supplement of iron protein succinylate should be considered in the therapy of HD caused by IDA (193) due to its less adverse than iron-infusion.

In a randomized, double-blind, placebo-controlled clinical study of early menopausal women succinate-based composition treatment of mice has shown restoration of the estrous cycle and increase in the weight and calcium content of bone tissue (194). Additionally, in a randomized, placebo-controlled clinical trial in menopausal women, a succinate-based combination therapy substantially decreased most subjectively evaluated characteristics of menopausal syndrome and enhanced blood serum levels of estradiol fourfold.

It has also relieved hot flushes and headache symptoms (194).

11. Polysaccharides

Polysaccharides, possessing a broad range of biological functions, are polymeric carbohydrates consisting of more than ten monosaccharide units, which are linked together by glycoside bonds (195). Common examples of polysaccharides are glycogen, chitin, chitosan, starch, cellulose, agarose or pectin (196).

WDT contains Portae sclerotium Cocos algae Polysaccharides (PCPs) as a bioactive component (2). PCPs are the most abundant substances in Poriae sclerotium cocos albae, also known as Fu Ling in Chinese, which is an edible medical fungus (197). Traditionally Fu Ling has been used for medicinal purposes for more than thousand years (198). The pharmacological actions of PCPs in Fu Ling include antibacterial, anti-tumor, anti-hyperglycemic, immunomodulative, anti□inflammatory, immunostimulatory, anti-oxidative, anti□ageing, anti-hepatic, anti-diabetic and anti-hemorrhagic fever effects (196, 197, 199, 200). Additionally, Sun et al. showed in their study that PCPs improved hyperglycemia, hyperlipidemia and hepatic steatosis in mice (201).

PCPs find applications in cancer therapy and many other diseases. They have been described to reduce tumor growth and improve antioxidant enzyme activity, when fed daily for 7 weeks in Wistar rats (202). As PCPs have anti-tumor cell proliferation effect and inhibit tumor growth (203, 204) their medical administration might be beneficial to the treatment of secondary headache caused by one or more space-occupying intracranial tumors ICHD-3 7.4.1 (20).

The polysaccharide from the Poria cocos (accepted name: Poriae sclerotium cocos albae) was shown to improve hyperglycemia, hyperlipidemia and hepatic steatosis via modulation of gut microbiota (201). An enhancement of gut microbiota and decline of inflammatory factors can have positive effects on improving gut and brain function. Additionally, it is suggested that probiotics might have a beneficial effect in reducing the frequency and severity of migraine attacks. Worth mentioning that similar to migraine, disorders of the brain involving depression and anxiety have been demonstrated to be associated with increased gut permeability (205) and probiotics boosting gut microbiota help to decrease gut permeability and prevent leaky gut syndrome (206).

In 2015, PCPs have received approval from the Chinese Food and Drug Administration for treating various types of diseases like cancer, hepatitis alone or during chemoradiation therapy for cancer patients (196).

12. Conclusion

Research regarding bioactive compounds of WDT is very rare. Based on our research information only Zhang et al. (2) and Wu et al. (29) have examined the bioactive compounds of WDT in their studies so far. To our best knowledge, no clinical trial has been done regarding the treatment of any type of headache with WDT. Therefore, this study approached to explore the pharmacological reaction of the API containing in WDT associated with HD.

The current study gathers information on WDT compounds, which can be used as a guideline for physicians to help HD patients' and improve their QoL. The alkaloid p-synephrine has potential to reduce primary and secondary headache caused by rhinitis patients through its vasoconstrictive characteristics. By increase of fat burning rate and the expected weight loss p-synephrine could also contribute to life quality improvement of obesity patients and related migraine headaches. Gingerols is promising to have a positive effect in reducing migraine through their anti-oxidative effect, inhibitory effect on controlling prostaglandin biosynthesis induced migraine through the inhibition of prostaglandin biosynthesis and in working against hypoglycemia-caused migraine by increasing glucose transport into muscle cells. Isoflavones can contribute to the control of migraine caused by increased estrogen levels as well as menstrual associated migraine. The isoflavonoids liquiritin and liquiritingenin might exert a positive effect on Interleukin 1β induced headache. Liquiritin shows potency to have a beneficial effect on menstrual related migraine and nausea through inhibition of progesterone metabolism. Liquiritigenin's antidepressant and anxiolytic effects are expected to positively contribute to life quality improvement of HD patients. Hypoglycemic activity of pachymic acid exerts a positive effect against diabetes-caused secondary headache, whereas succinate-based composition is helpful in controlling general menopausal and specifically headache symptoms by restoring estrous cycle. Polysaccharides PCPs can contribute to migraine control by its anti-oxidative, anti-inflammatory, and anti-tumor effects and as probiotics enhancing gut microbiota composition.

These findings provide some hints that WDT as a combination of these API might be beneficial in the treatment of several diseases, particularly, for patients with HD. Up to date there is no sufficient clinical research investigating the pharmacological effects and the mechanisms of action of WDT. Consequently, more clinical trials are needed to gain more understanding in the treatment of HD with WDT.

High quality clinical research over a long period with larger patients' group should be carried out to evaluate the therapeutic effectiveness of WDT in HD to investigate, if WDT could be a suitable prescription for people with HD, especially in migraine and TTH.

Our study lacks all the other clinical trials done for various diseases other than HD. Moreover, the effect sizes of the API in WDT were not carried out to investigate the etiopathogenetic mechanism of WDT. Nevertheless, our article contains HD as primary and secondary disorder to other pathologies. Thus, it brings a broader spectrum of herbal use for therapeutic and prophylactic treatment

for all types of HD.

This manuscript is collective evidence to address the multipotency of WDT and their bioactive components in detail. In conclusion this study arises a question for a conclusive clinical trial of WDT with large samples for patients for treating migraine and tension-type headache.

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