SOUTH BAYLO UNIVERSITY

Efficacy of Herbal Formulas on Sleep Disorder

by

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A RESEARCH PROJECT SUBMITTED

IN PARTIAL FULFILLMENT OF THE

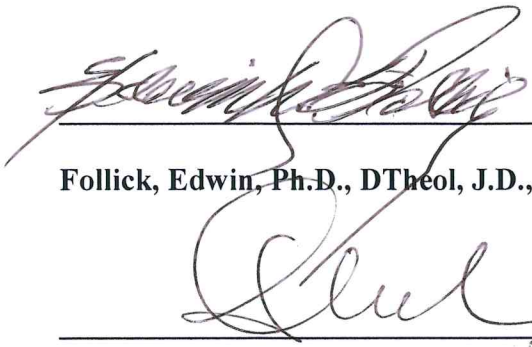
REQUIREMENTS FOR THE DEGREE

Doctor of Acupuncture and Oriental Medicine

ANAHEIM, CALIFORNIA

JUNE 2017

THE RESEARCH PROJECT OF SAEROM OH
APPROVED BY RESEARCH PROJECT COMMITTEE



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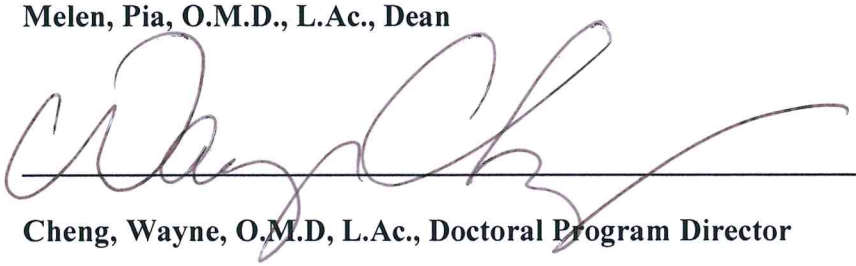

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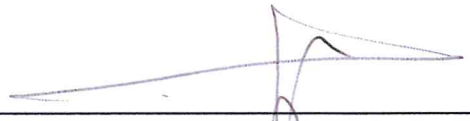

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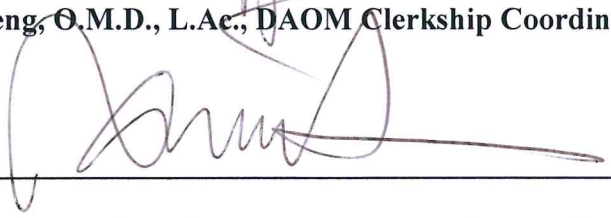

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ANAHEIM, CALIFORNIA

JUNE 20, 2017

Efficacy of Herbal Formulas on Sleep Disorder

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SOUTH BAYLO UNIVERISTY AT ANAHEIM, 2017

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ABSTRACT

Sleep is essential for a person's health and well-being, according to the National Sleep Foundation (NSF). Yet millions of people do not get enough sleep and many suffer from lack of sleep. Because of importance of sleep, pharmacological approaches have been included in conventional medical treatment for insomnia or sleep disorders. However, long-term use of frequently prescribed medications can often lead to habituation, critical withdrawal symptoms and/or side effects. Some individuals with insomnia or trouble sleeping have used complementary and alternative medicine (CAM) therapies which include acupuncture and oriental medicine, to treat their conditions. Recently, CAMs or herbs have been noticed as a natural solution for their sleep problem.

Therefore, this literature review is to determine the efficacy of herbal medicine on sleep disorder. The searching keywords were "Insomnia", "Sleeping Disorder "or "Sleep" and "Oriental medicine" or "Herbal Medicine" or "Chinese Medicine" or "Traditional Chinese Medicine". Total of 11 clinical trials with 1609 participants that were done from January 2001 to December 2016 were reviewed and most of the studies showed efficacy of herbal medicine in sleep disorder treatment.

The outcomes were measured by scores of PSQI-Pittsburg Sleep Quality Index, CES-Clinical Effective Survey, SD-Sleep Diary, ISI-Insomnia Severity Index, STAI-State Trait Anxiety Inventory, DBI-Beck Depression inventory. .

Although many of studies proved efficacy of herbal medicine on sleep order, larger sample size and longer study time randomized control trials and comparison between western and TCM theories are required.

Key words: herbal medicines, insomnia, sleep disorder

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I. INTRODUCTION

The needs for the proper quantity and quality of sleep are same as hunger and thirst. Human sleep approximately one-third of their lives and sleep plays a vital role in health and well-being throughout the life. Sleep is involved in healing and repairing of the heart and blood vessels.[1] Ongoing sleep deficiency is linked to an increased risk of heart disease, kidney disease, high blood pressure, diabetes, and stroke. Sleep deficiency also increases the risk of obesity. Because, sleep maintains a healthy balance of the hormones that makes a person feel hungry (ghrelin) or full (leptin). When a person does not get enough sleeping, the level of ghrelin goes up and level of leptin goes down, which make a person feel hungrier than when a person is well-rested.[2]

Sleep also supports healthy growth and development as well as immune system.[3] The benefit and importance of quality sleep are very certain and important for quality of human life. Due to this fact, pharmacological approaches and research have been made for decades. [4] Recent research has led to a substantially improved understanding of both normal and altered sleep patterns.

Definition of sleep in medicine is a period of rest for the body and mind, during which volition and consciousness are in partial or complete abeyance and the bodily functions partially suspended[5], which are triggered by a complex group of hormones that are active in the main, and that respond to cues from the body itself and the environment. About 80% of sleep is dreamless, and is known as non-rapid eye movement (NREM) sleep.[6] Sleep has also been described as a behavioral state marked by

characteristic immobile posture and diminished but readily reversible sensitivity to external stimuli.[7]

Because of importance of sleep, pharmacological approaches have been included in conventional medical treatment for insomnia or sleep disorders. [8] However, long-term use of frequently prescribed medications can often lead to habituation, critical withdrawal symptoms and/or side effects.[9] Some individuals with insomnia or trouble sleeping have used complementary and alternative medicine (CAM) therapies which include acupuncture and oriental medicine, to treat their conditions.[10]

1. Etiology of Sleep disorder in Western Medicine

Sleep disorder can be categorized in to three terms based on duration. Transient insomnia is often self-limited and usually lasts no longer than 7 days; short term insomnia lasts for 1 to 3 weeks; and chronic insomnia lasts longer than 3 weeks. Chronic insomnia is usually associated with medical, psychiatric, psychological, or substance-use disorders.

Changes in sleep architecture are common with advancing age. Sleep initiation is more difficult in the elderly, and waking earlier than planned is also common in the elderly (age of 65 and more) [11]. Changes in the circadian rhythm caused by the normal aging process dictate patterns of falling asleep and waking up earlier.

Insomnia can be caused by stress or by disturbances in the normal sleep-wake cycle. Comorbidities such as physical disability, respiratory problems, medication use, depressive symptoms, environmental factors, poor living conditions, and loss of a spouse, close friend, or relative have all been associated with higher rates of insomnia in individuals over the age of 65. Conditions such as depression, anxiety, asthma, chronic obstructive pulmonary disease, congestive heart failure, thyroid disease, gastroesophageal

reflux disease, pain, sleep apnea, and neurologic disorders also are linked to the development of insomnia. Depression and dementia, which are quite common in the elderly, have been associated with sleep disturbances in this population.

Several types of medications have been known to cause insomnia in older people. These include central nervous system (CNS) stimulants (diet pills or amphetamines), antidepressants, corticosteroids, diuretics, anticonvulsants, and certain antihypertensives (e.g., beta-adrenergic blockers). Additionally, alcohol and nicotine can have a profound negative effect on the quality and quantity of sleep.

Table 1. Cause of Insomnia

Medical and Psychiatric	Iatrogenic	Psychosocial
Anxiety disorder	Alcohol	Bereavement
Asthma/COPD	Beta-clockers (nightmares)	Financial stress
Bipolar disorder	Caffeine	Jet lag
Dementia	Diuretics (nocturia)	Marital difficulties
Depression	Drug (cocaine) abuse	Personal conflicts
Menopause	Nicotine	Poor sleep hygiene
Sleep apnea	SSRIs	Night shift
Thyroid disease	Steroids	Work-related stress

2. Treatment of Sleep disorder in Western Medicine

There are psychological and behavioral techniques (non-medical) that can be applied to improve sleep disorder. This includes relaxation training, stimulus control, Cognitive behavioral therapy (CBT). Often time, OTC drugs are recommended with non-medical

therapy, which includes Diphenhydramine and doxylamine. These drugs are ethanolamine derivatives with potent histamine$_1$ (H_1) receptor antagonist activity and anticholinergic properties to improve their sleep.[12] The other popular OTC drug would be melatonin. Melatonin is an endogenous hormone secreted by the pineal gland that may have some utility in treating circadian rhythm-based sleep disorders. [13]

The last option is the prescription medication. There are Benzodiazepines, Non-benzodiazepine Hypnotics and Tricyclic Antidepressants.

Table 2. Prescribed medication for Insomnia

Benzodiazepines	Non-benzodiazepine	Anti-depressant
Triazolam	Zolpidem	Trazodone
Estazolam	Zaleplon	Doxepin
Temazepam	Eszopiclone	
Flurazepam	Ramelteon	
Quazepam		

2. Etiology of Sleep disorder in Oriental Medicine

Insomnia is a manifestation of a Shen(神) disorder which various internal disharmonies makes the Shen restless and thus create sleeping problem.

According to the study "Classification of Insomnia using the Traditional Chinese Medicine System: A Systemic Review."[14], the most common TCM causes of sleep disorder were deficiency of both the heart and spleen (心脾**兩**虛), hyperactivity of fire due to yin deficiency (陰虛火旺), liver-qi stagnation transforming into fire (肝鬱化火),

heart-kidney non-interaction (心腎不交), qi deficiency of heart and gallbladder (心膽氣虛), internal disturbance of phlegm-heat (膽熱內擾), liver fire flaming upward (肝火上擾), heart deficiency with timidity (心虛膽怯), stomach disharmony (胃脾不和) and stomach qi disharmony (胃氣不和).

This study will discuss 1,609 clinical trials on the efficacy of herbal medicine only in patient with sleep disorder with use of Gui Pi Tang for deficiency of both the heart and spleen (心脾兩虛), Huang Lian Jie Du Tang for liver-qi stagnation transforming into fire (肝鬱化火), Tian Wang Bu Xin Dan for heart-kidney non-interaction (心腎不交), Suan Zao Ren Tang for qi deficiency of heart and gallbladder (心膽氣虛), Wen Dan Tang for internal disturbance of phlegm-heat (膽熱內擾), Shao Yao San for liver fire flaming upward (肝火上擾) and Liu Jun Zi Tang for stomach disharmony (胃脾不和).

The result of herbal medicine treatment on subject with sleep disorder will be analyzed. The studies show that herbal medicine efficacy in helping sleep disorder patients by showing the score before and after treatment in many aspects such as sleeping quality, time to fall asleep, total sleep hours and scores of PSQI-Pittsburg Sleep Quality Index, CES-Clinical Effective Survey, SD-Sleep Diary, ISI-Insomnia Severity Index, STAI-State Trait Anxiety Inventory, DBI-Beck Depression inventory.

II. MATERIALS & METHODS

2.1 Search Strategy

Following databases were used from January 2001 to December 2016 to identify trials; PubMed, Web of Science, Embase Cochrane Library, Korean TK, China knowledge Resource Integrated and Medline. The searching keywords were ("insomnia", "sleeping disorder" or "sleep") and ("Oriental Medicine" or "Herbal Medicine" or "Chinese Medicine or Traditional Chinese Medicine" or "TCM"

2.2 Inclusion Criteria of studies

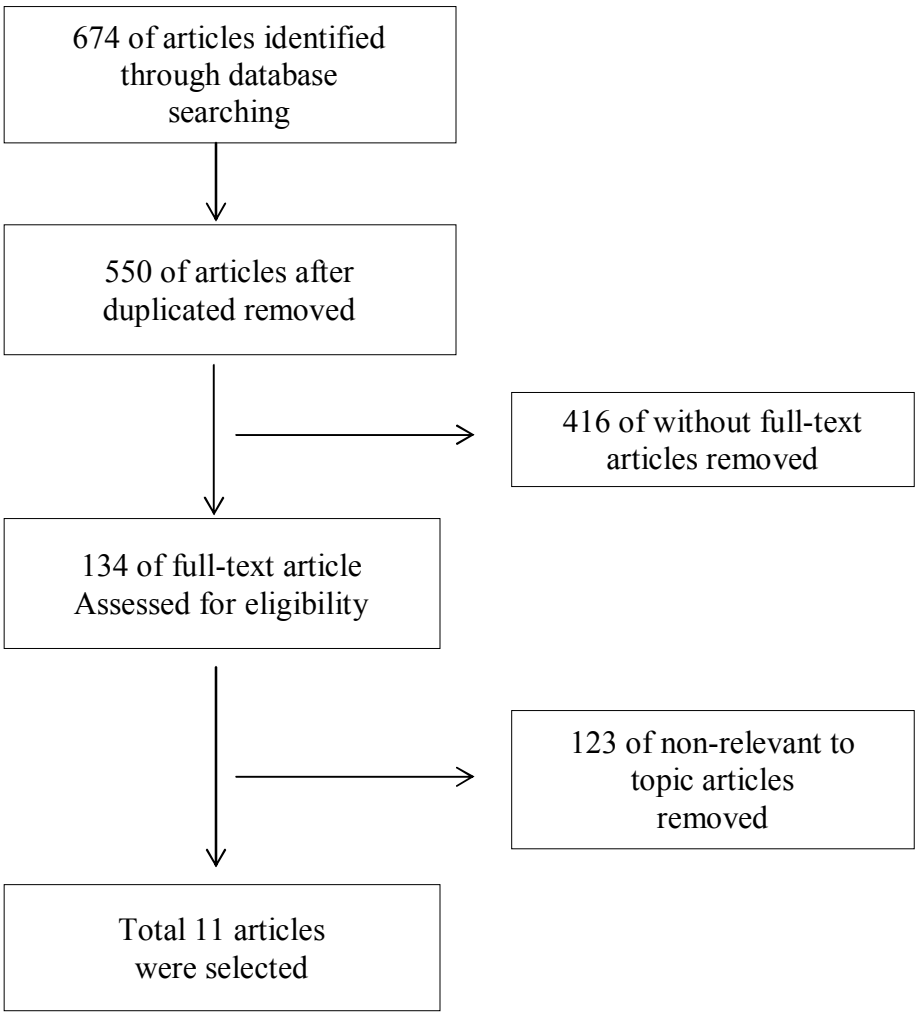
This study only reviewed and included research that compared combinations of Herbal Medicine and sleep disorder or insomnia alone. Also, a research that was published as full-text articles, and contains sufficient and reliable information on their methods and outcomes were selected for this study.

Figure 1 represents the search and selection procedure and exclusion and inclusion criteria for the articles.

Table 3. Exclusion and Inclusion Criteria

	Excluded	Included
Database	0	674
Duplicated	124	550
Full-text article	416	134
Relevant to topic	123	11

Figure 1. Research and selection of Articles process



III. RESULTS

3-1. Results of the Literature Search

11 clinical trials with 1,609 participants were included. They were performed in South Korea and Hong Kong. Sample size from 3 to 1376 with insomnia that meet the diagnosis of insomnia was classified under Diagnostic and Statistical manual of Mental Disorders – Text Revision 4th ed. (DSM-IV-RT).

As mention above, the outcome was measured by PSQI- Pittsburg Sleep Quality index, CES-Clinical Effective Survey, SD- Sleep Diary, ISI-Insomnia Severity Index, STAI - State Trait Anxiety Inventory, BDI – Beck Depression inventory.

Moreover, statistic numbers and evidence such as demographic and clinical characteristics will be shown in the table, figures and flow charts. Result with p-value of 0.05 or less are considered significant.

Table 4. Summary of the case studies that were selected

Author	Formula	Participants	Outcome Measurement
Park 2011[15]	Gui Pi Tang	156	CES, SD
Seok 2006[16]		1	CES, SD
Go 2006[17]		1	SD
Ryu 2001[18]	Huang Lian Jie Du Tang	3	CES, SD
Lee 2013[19]	Tian Wang Bu Xin Dan	29	ISI
Xi 2013[20]	Suan Zao Ren Tang	1323	PSQI
Hong 2004[21]		30	CES
Kim 2007[22]	Wen Dan Tang	5	ISI
Park 2011[23]		3	ISI,STAI,BDI

Jae2011[24]	Shao Yao San	2	CES
Kim 2010[25]	Liu Jun Zi Tang	3	ISI

Abbreviations: PSQI- Pittsburg Sleep Quality index,CES-Clinical Effective Survey, SD- Sleep Diary, ISI-Insomnia Severity Index, STAI - State Trait Anxiety Inventory , BDI – Beck Depression inventory

3-2. Intervention and Comparing

3-2-1. Gui Pi Tang – Park 2011

This study was to investigate clinical usage of Gui Pi Tang on sleep disorder patients who were diagnosis with deficiency of both the heart and spleen. The study contains 156 clinical trials from 2007 to 2008. The Clinical Effective Survey was used as an outcome measurement. Each survey was recorded by physicians at the hospital.

Table 5. Before and after of the study

Result	Before treatment	After treatment
Excellent	n = 0 (0%)	n = 16 (10.2%)
Good	n = 45 (28.8%)	n = 96 (61.6%)
No remarkable change	n = 80 (51.2%)	n = 26 (16.7%)
Failure	n = 31 (20%)	n = 18 (11.5%)
Total participant	n = 156	

3-2-2. Gui pi Tang –Seok 2006

This case was on 59 years old male Vietnam War veteran who was a diagnosed with deficiency of both the heart and spleen and had severe symptoms of anxiety, agitation, thirst and chronic constipation along with the insomnia. The study showed improvement on not only the insomnia but also on neuropsychiatric symptoms within a month.

Table 6. Before and after of the study

Tests		Before	After
SCL-90-R	SOM	59	41
	O-C	66	35
	I-S	45	36
	DEP	70	43
	ANX	59	40
	HOS	44	42
	PHOB	51	48
	PAR	48	38
	PSY	57	43
Beck Depression Inventory		25 (Moderate)	14 (Mild)
Zung's Self Rating Depression Scale		63 (Severe)	52 (Moderate)
Total Sleep hours		4 hours	7.5 hours
Time to Fall asleep		20 minutes	10 minutes
Restless		1-3	None-3

Som: Somatizion, **O-C :** Obssessive-Compulsive**, I-S:** Interpersonal Sensitiviy**, DEP:** Depression**, ANX:** Anxiety, **HOS:** Hostility, **PHOB:** Phobic Anxiety, **PAR:** Paranoid Ideation, **PSY:** Psychoticism

3-2-3. Gui Pi Tang – Go 2006

This case was on 40 years old female housewife who was a diagnosed with deficiency of both the heart and spleen and had a severe insomnia from an incident that caused too much stress. She has been taking prescribed drug "Alprazolam" for a month. Because of no changes in her condition, she wanted to try Oriental Medicine for her symptom. The study showed improvement on sleep hours after a one month of treatment.

Table 7. Before and after of the study

Tests	Before	After
Total Sleep hours	1 hour	6 hours
Subjective satisfactory	very unsatisfied	satisfied

3-2-4. Huang Lian Jie Du Tang – Ryu 2001

This study reviewed 3 clinical trials on stroke patients who were diagnosed with Liver-qi stagnation transforming into fire and excessive heat-fire syndrome and had symptoms of insomnia along with dizziness, night chest discomfort. The length of trials was 2 weeks. Even with this short period of time, the score and total hours of sleep has been improved.

Table 8. Before and after of the study

Case	Tests	Before	After
Case # 1	4 – ordinal scale	3	0
	Time to fall asleep	5 hours	0.5 hours
	Total sleep hours	1 hour	4.5 hours
Case # 2	4- ordinal scale	3	0
	Time to fall asleep	1 hour	2 hours
	Total sleep hours	0 hour	6 hours
Case # 3	4 – ordinal scale	3	1
	Time to fall asleep	0.5 hour	2.5 hours
	Total sleep hours	0.2 hour	5 hours

4-oridinal scale (0=no, 1=slight, 2=moderate,3=severe)

3-2-5. Tian Wang Bu Xin Dan – Lee 2013

This study reviewed 12 male, 17 female patients who were diagnosed with heart-kidney

non-interaction. Mean age of participants was 62.9 (min.47, max.77). 18 participants were complaining of difficulty falling asleep, 22 of difficulty staying asleep, 16 of problem waking up too early (overwriting available). The length of trials was 4 weeks. Baseline of ISI score was 18.1, which means clinical insomnia, and score of after treatment was 7.5, which means no clinically significant insomnia.

Table 9. Before and after of the study (*p< 0.005)

	Before Treatment	After Treatment	P value
Mean score of ISI	18.1	7.5	0.000*

3-2-6. Suan Zao Ren Tang – Xi 2013

Suan Zao Ren Tang versus Conventional Medication

In this study, there were 8 RCTs comparing Suan Zao Ren Tang monotherapy with conventional medicine. Benzodiazepine was the only Western medication comparator. The clinical effective rates in the Suan Zao Ren groups varied from 90% to 96.7%, with a mean of 92.5%. While the clinical effective rates in the benzodiazepine groups ranged from 66.7% to 93%, with a mean of 78.9%. Based on the sleep questionnaires, one of 8 RCTs reported significant effects of Suan Zao Ren Tang therapy for improving PSQI score when compared with 5 mg diazepam ($p < 0.05$); one RCT reported for improving score of Spiegel sleep questionnaires ($P < 0.05$) when compared with estazolam ($p < 0.05$). the other RCT reported that 90 days follow up was done to gather the information of patients' sleep rebound time at the end of the 15 days of this study, and the results indicated that time to onset in Suan Zao Ren group was significantly slower than in estazolam group.

Table 10. Comparison of conventional Medicine vs Suan Zao Ren Tang

	Participants	Improvement % after tx
Suan Zao Ren Tang Group	779	92.5%
Benzodiazepine Group	544	78.9%

3-2-7. Suan Zao Ren – Hong 2005

This study reviewed 6 male, 20 female patients who were diagnosed with Qi deficiency of heart and gallbladder. Mean age of participants was 63.15. The length of trials was 3 months and total sleep time was increased by 1.75 ± 2.23, delaying time before sleep was decreased by 1.57 ± 2.50, and awake time during sleep was decreased by 0.96 ± 1.46.

Table 11. Before and after of the study (*p< 0.004)

	Before treatment	After treatment	P-Value
Mean of total Sleeping time	4.05 ± 1.87	5.80 ± 1.88	0.001
Mean of delaying time before sleep	2.69 ± 2.45	1.12 ± 0.97	
Mean of awake time during sleep	3.42 ± 1.81	2.50 ± 1.10	0.004

Table 12. Subjective Satisfactory

Result	Before treatment	After treatment
Excellent	n = 0 (0%)	n = 1 (3.8%)
Good	n = 5 (19.2%)	n = 15 (57.7%)
No remarkable change	n = 15 (57.7%)	n = 8 (30.8%)
Failure	n = 6 (23.1%)	n = 2 (7.7%)
Total participant	n = 26	

3-2-8. Wen Dan Tang – Kim 2007

This study reviewed 3 male, 2 female chronic insomnia patients who were diagnosed with internal disturbance of phlegm-heat. Mean age of participants was 49.8. The length

of trials was 6 months. Mean of total sleep time was increased by 2.2 hours and frequency of awake during sleep was improved by 96%.

Table 13. Before and after of the study

Case	Tests	Before	After
1	Total Sleep Hours	3 hours	8 hours
	Awake times during sleep	2 time	0 times
	ISI score	24	6
2	Total sleep hours	2-3 hours	6 hours
	Awake times during sleep	3-4 times	0 times
	ISI score	26	10
3	Total sleep hours	4 hours	5 hours
	Awake times during sleep	2 times	0 times
	ISI score	18	8
4	Total sleep hours	4 hours	6 hours
	Awake times during sleep	2 times	0 times
	ISI Score	24	8
5	Total sleep hours	5-6 hours	4-5 hours
	Awake times during sleep	4-5 times	0-1 times
	ISI Score	22	12

3-2-9. Wen Dan Tang – Park 2011

This study was done on 3 female insomnia patients with more than 15 points on Insomnia Severity Index scale and diagnosed with internal disturbance of phlegm-heat. These 3

participants were assessed using SCL-90-R, STAI, STAXI, and BDI. After 2 weeks of herbal treatment, quality of sleep has improved and score on ISI, STAI, STAXI,BDI were decreased.

Table 14. Scores of before and after treatment

Test	Case	Before treatment	After treatment
STAI-S	1	73	53
	2	70	46
	3	42	28
STAI-T	1	69	65
	2	68	53
	3	38	27
STAXI- S	1	14	14
	2	15	13
	3	10	10
STAXI-T	1	19	18
	2	32	21
	3	15	10
STAXI-Expression Control	1	25	22
	2	14	18
	3	30	20
STAXI- Expression out	1	16	14
	2	24	15
	3	8	8
STAI-Expression in	1	14	12
	2	23	21
	3	12	9
BDI	1	33	28
	2	43	19
	3	12	11
ISI	1	24	15
	2	18	4
	3	23	12

STAI: State-Trait Anxiety Inventory, **STAXI:** State-Trait Expression Inventory, **BDI:** Beck Depression Inventory, **ISI :** Insomnia Severity Index

3-2-10. Shao Yao San – Jae 2011

This study was done on 2 female insomnia patients who were diagnosed with Liver fire flaming upward. The length of study was 7 weeks and both quality of sleep was improved and score for depression was decreased.

Table 15. Clinical Sleep Survey

Test	Case #	Before treatment	After treatment
Subjective Satisfactory	1	Unsatisfied	Very satisfied
	1	Unsatisfied	Very satisfied
Score of HRSD	2	17	6
	2	18	5

HRSD: Hamilton Rating Scale for Depression

3-2-11. Liu Jun Zi Tang – Kim 2010

This study was done on 3 female insomnia patients who were diagnosed with stomach disharmony. The length of study was 7 days. Within this short period time, this study provided improved score of Insomnia Severity Index. Although restless sleep did not changed, total sleep time and time to fall asleep were improved.

Table 16. Before and after of the study

Test	Case	Before treatment	After treatment
ISI Score	1	27	4
	2	26	5
	3	18	7
Total Sleep Time	1	2 hours	7 hours
	2	2 hours	7 hours
	3	1-2 hours	6 hours
Time to Fall asleep	1	60 minutes	0 minutes
	2	30-60 minutes	0 minutes
	3	60-120 minutes	0 minutes
Restless Sleep	1	1 times	1 times
	2	4-5 times	1 times
	3	1 times	2 times

V. DISSCUSION

1. Interpretation of Principal Findings

This study found statistically pooled benefits of herbal formulas on sleep disorder cases. Most of clinical trials show significant improvement on scores of questioners or clinical sleep diaries that were recorded by physicians.

2. Weakness of the study

The 11 studies that were selected were not Randomized Control Trials model studies. Even though, they were case studies, they did have many participants to compensate the lack of having control group. However, since there is no control group to compare, this might show as not strong enough evidence to prove the efficacy on herbal medicine.

This study found that terminology relating to sleep-related symptoms in the TCM classification was much more detailed than those used in the Western diagnostic systems. [26] The insomnia symptoms mentioned in the Diagnostic and Statistical manual of Mental Disorders 4th edition [27] and the WHO international Classification of Diseases 10th edition [28] include difficulty falling asleep, difficulty maintaining sleep, non-refreshing sleep, and non-restorative sleep. Although excessive dreaming, awakening with a start and restless sleep were common complaints in individuals with insomnia, they were not utilized in the Western Medicine diagnostic systems. Half asleep, gong to sleep late at night, insomnia with vexation, and difficulty falling asleep with vexation was seldom mentioned in the Western Medicine literature.[29]

This study includes examination of sleep-related, non-sleep-related, tongue, and

pulse features of the most common presented TCM diagnosis. Many of articles include different terminologies relating to sleep-relate symptoms, but have same/similar meaning. For example, 8 different Chinese terminologies were used to describe difficulty falling asleep and 4 different Chinese terms describing insomnia.[30] Also, most sleep-related symptoms appeared in more than one TCM diagnosis. For example, excessive dreaming and difficulty falling asleep were found in 7 of the 10 most commonly presented TCM diagnosis patterns, while difficulty staying asleep was presented in 5 of top 10 TCM diagnosis patterns.[31]

Therefore, it is very difficult to put each case into just one TCM diagnosis categories as many cases include more than a one TCM diagnosis pattern. Because of this fact, it is very common to customize the composition of original formula to each case. Moreover, there are many formulas that can be applied to the same TCM diagnosis. For example, this study used Gui Pi Tang for deficiency of both the heart and spleen, but Zi Yin Jian Pi Tang is another popular formula for that diagnosis.[32] It needs more studies to find out which formula works better with same TCM diagnosis.

V. CONCLUSION

Herbal medicine is just as much popular treatment method as acupuncture in Oriental medicine. Because of the complexity of herbal formulas and many obstacles to make herbal decoction in United States, not many studies have been done on herbal medicine. Even though lack of RCTs model studies was included, but 96.7% from 1,609 participants clearly showed improvement on their sleep disorder and none of them had a side-effect from the herbal medicine.

Despite the limitations, this study systematically summarized important data on efficacy of herbal formula on sleep disorder. While the TCM classification system had the potential to refine treatment by identifying subtle differences in etiology, pathogenesis, and body constitution, a lack of standardization in terminology, composition of herbal formulas and consensus on diagnostic criteria are major barriers.

Nevertheless, due to these barriers, more effort on standardization in TCM diagnostic systems and protocol is required. Also, larger sample size and longer study time randomized control trials and comparison between western and TCM theories are strongly recommended.

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