REVIEW ARTICLE

pISSN 1226-6396, eISSN 2234-4942
J of Oriental Neuropsychiatry 2021;32(2):95-109
https://doi.org/10.7231/jon.2021.32.2.095

JON Journal of Oriental Neuropsychiatry

Suggestions for Potentially Useful Herbal Medicines for Treating Insomnia in COVID-19 Era: A Mini-Review

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Received: May 21, 2021
Revised: June 16, 2021
Accepted: June 25, 2021

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Acknowledgement
This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant Number: HF20C0079).
The authors are grateful for the support of the COVID-19 telemedicine center of Korean medicine, the Association of Korean Medicine, and the research team for the Korean medicine clinical practice guidelines for insomnia (version 1.0).

Objectives: The coronavirus disease 2019 (COVID-19) has become a global pandemic. Mental sequelae occurring in patients with COVID-19 and the general population are important concerns. In Korea, herbal medicine is used nationwide to respond to this pandemic. It can be prescribed by COVID-19 telemedicine center of Korean medicine (KM). Among some herbal medicines, *Gamiguibi-tang* is the only herbal medicine prescribed for individuals with mental health, especially for those with insomnia. In this mini-review, the objective of this study was to summarize the evidence of some promising herbal medicines available for treating primary insomnia based on existing clinical and preclinical studies.
Methods: A research team was formed for KM clinical practice guidelines for insomnia (version 1.0). Team members were provided with a list of references of relevant herbal medicines for insomnia. To gather evidence from clinical studies with appropriate sample sizes, among the list of references, randomized controlled trials for primary insomnia that included 50 subjects or more per arm and used herbal medicine were included in the final analysis. Moreover, pre-clinical studies examining the mechanism of action of each herbal medicine and studies on herb-drug interactions, were searched and summarized.
Results: Four herbal medicines (*Ondam-tang, Sanjoin-tang, Guibi-tang,* and *Hyeolbuchugeo-tang*) were reviewed based on existing clinical and preclinical studies. Based on findings of existing studies, some suggestions of herbal medicines for insomnia in the COVID-19 era in Korea were suggested.
Conclusions: Data of this study could be used to prepare a future revision of the manual of COVID-19 telemedicine center of KM.

Key Words: COVID-19, East asian traditional medicine, Herbal medicine, Insomnia, Mental health.

I. INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by infection with a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic[1]. Currently, the development of some vaccines against COVID-19 raises expectations of liberation from the pandemic. However, mental sequelae occurring in SARS-CoV-2-infected patients as well as in the general population, have become an important concern[2]. A recent systematic review found that more than 1 in 5 healthcare workers experienced anxiety and depression during the COVID-19 pandemic, and the estimated prevalence of insomnia was about 40%[3]. Moreover, depression was observed in about 30% of patients with COVID-19[4]. Another study analyzed 17,865 active Weibo users and found that negative emotions, such as anxiety, depression, and indignation, increased and positive emotions, such as happiness, decreased during the pandemic[5]. Even before this pandemic, large-scale disasters often had a negative impact on human mental health[6]; in particular, infectious diseases can have a greater impact on the mental health of humans, as they have to live with curtailed liberties and amid long-term uncertainty[7].

In China, traditional Chinese medicine (TCM) has been used to respond to this pandemic. Based on favorable evidence for severe acute respiratory syndrome (SARS)[8], interest in TCM has increased during this pandemic. Korean medicine (KM), a type of East Asian traditional medicine (EATM), along with TCM, is also being used in Korea to solve health problems related to COVID-19. In Korea, which has been relatively early affected by the pandemic, the COVID-19 telemedicine center of KM was established by the Association of Korean Medicine (AKOM), on March 9, 2020, and it has been treating more than 20% of the country's patients through its telemedicine service[9] (Fig. 1). In this center, volunteer KM doctors listen to the symptoms of individuals and prescribe appropriate herbal medicines according to the existing manual (i.e. COVID-19 Korean medicine clinical guidance)[10]. According to this manual, *Gamiguibi-tang* is the only herbal medicine appropriate to improve the mental health condition of individuals, which is also prescribed for insomnia. The administration of *Gamiguibi-tang* was proposed based on the KM clinical practice guidelines for insomnia (version 1.0; not officially published), developed by the Korean Society of Oriental Neuropsychiatry.

However, in order to broaden the options of herbal

Fig. 1. COVID-19 telemedicine center of KM.

medicine for insomnia in the future, the authors collected clinical and pre-clinical evidence for other herbal medicines that could potentially be used for COVID-19-related insomnia, for future revision of treatment guidelines for the COVID-19 telemedicine center of KM.

II. MATERIALS AND METHODS

1. Selection of candidate herbal medicine for insomnia

We requested a research team for the KM clinical practice guidelines for insomnia (version 1.0) and were provided with a list of references of relevant herbal medicines for insomnia. To gather evidence from clinical studies with appropriate sample sizes, among the list of references, randomized controlled trials (RCTs) for primary insomnia that included 50 subjects or more per arm and used herbal medicine[11] were included in the analysis. As results, the five types of herbal medicines (*Ondam-tang*, *Sanjoin-tang*, *Soyo-san*, *Guibi-tang*, and *Hyeolbuchugeo-tang*) suggested in this guideline were considered. However, *Soyo-san*, which was not tested in an RCT with 50 subjects or more per arm, was excluded.

2. Data analysis

In the RCTs for primary insomnia that included 50 subjects or more per arm and used *Ondam-tang*, *Sanjoin-tang*, *Guibi-tang*, and *Hyeolbuchugeo-tang*, the study design, population, sample size, type of herbal medicine, comparator, type of pattern identification, duration of the treatment, results, and safety profiles were extracted and summarized (Table 1). Moreover, pre-clinical studies examining the mechanism of action of each herbal medicine, as well as the study of herb-drug interactions, were searched and summarized by two researchers (HWS and CYK). The researchers also extracted the animal models used in the experiments and the results of the studies (Table 2).

III. RESULTS

1. *Ondam-tang*

1) Preclinical evidence

According to some preclinical studies, *Ondam-tang* exerted anti-stress effects by modulating the levels of neurotransmitters such as epinephrine, norepinephrine, dopamine, and serotonin in stress-induced mouse and rat models[12,13]. Moreover, the herbal medicine was effective in improving negative emotion-related behaviors by upregulating orexin-A and leptin expression in a sleep-deprived rat model (Table 2)[14].

2) Clinical evidence

There were nine large-scale RCTs comparing *Ondam-tang* and Western medicine (WM)[15-23]. The main WMs (used by 8/9 studies, 88.89%) were benzodiazepines, including diazepam and estazolam[15-19,21-23]. The remaining study used zopiclone[20]. In three of these studies[18,19,21], specific pattern identification was used to recruit participants, all of which were related to phlegm (痰). All studies had treatment periods of 2~4 weeks, and the most frequently used outcome was the total effective rate (TER)[15-23]. *Ondam-tang* showed significantly better results on TER than WM (8/9 studies, 88.89%)[15-20,22,23], except in one study that reported no significant difference[21]. In three studies[18,20,21], the global Pittsburgh Sleep Quality Index (PSQI) score was also reported as an outcome, but no significant difference was found between groups in two studies[20,21], while the remining study reported significantly lower scores in the *Ondam-tang* group[18]. Adverse events (AEs) were reported in six studies[15-18,20,21]; and in all studies, the incidence of AEs

Table 1. Characteristics of Included Randomized Controlled Trials

Comparison	Sample size (TG:CG)	Pattern identification	Duration	Results	Safety profiles	References
ODT vs. Diazepam 5 mg/day	113 (58:53)	NA	2 weeks	TER: HM＞WM*	HM: none WM: 16 (fatigue, drowsiness, dizziness)	15)
ODT vs. Diazepam 5 mg/day	120 (60:60)	NA	20 days	TER:HM＞WM+	HM: none WM: 12 (fatigue, drowsiness, dizziness)	16)
ODT vs. Diazepam 5 mg/day	120 (60:60)	NA	2 weeks	TER: HM＞WM (p-value was not presented)	HM: none WM: 19 (fatigue, forgetfulness, drowsiness, dizziness)	17)
ODT vs. Estazolam 1 mg/day	208 (112:96)	pattern of internal harassment of phlegm-heat (痰熱內擾)	4 weeks	TER: HM＞WM* PSQI global score: HM＜WM*	HM: 5 (fatigue, dry mouth, nausea) WM: 16 (cough, dry mouth, forgetfulness, fatigue, nausea, dizziness, anorexia)	18)
ODT vs. Estazolam 2 mg/day	140 (70:70)	pattern of binding and obstruction of phlegm and blood stasis (痰瘀交阻)	4 weeks	TER: HM＞WM^{+}	NR	19)
ODT vs. Zopiclone 7.5 mg/day	120 (60:60)	NA	4 weeks	TER: HM＞WM* PSQI global score: no significant difference	HM: 1 (heartburn) WM: 5 (bitter taste in mouth, dizziness)	20)
ODT vs. Estazolam 2 mg/day	120 (60:60)	pattern of internal harassment of phlegm-heat (痰熱內擾)	20 days	TER: no significant difference PSQI global score: no significant difference	HM: 3 (bitter taste in mouth, hyperhidrosis) WM: 5 (fatigue, drowsiness, dizziness)	21)
ODT vs. Estazolam 5 mg/day	120 (80:40)	NA	3 weeks	TER: HM＞WM^{+}	NR	23)
ODT vs. Estazolam 2 mg/day	120 (60:60)	NA	2 weeks	TER: HM＞WM*	NR	22)
ODT+Estazolam 2 mg/day vs. Estazolam 2 mg/day	120 (60:60)	pattern of internal harassment of phlegm-heat (痰熱內擾)	2 weeks	TER: IM＞WM*	IM: none WM: none	24)
ODT+Paroxetine 20 mg/day vs. Paroxetine 20 mg/day	126 (63:63)	pattern of internal harassment of phlegm-heat (痰熱內擾)	4 weeks	TER: IM＞WM* PSQI global score: IM＜WM* -Sleep latency, sleep duration, sleep efficiency, sleep disturbance, and daytime dysfunction: IM＜WM* HAMA: IM＜WM* HAMD: IM＜WM*	NR	25)
SJIT vs. Estazolam 2 mg/day	147 (78:69)	NA	4 weeks	TER: HM＞WM* Spiegel scale: HM＞WM*	NR	38)
SJIT vs. Estazolam 2 mg/day	144 (76:68)	NA	2 weeks	TER: HM＞WM* Spiegel scale: HM＞WM*	NR	39)
SJIT vs. Estazolam 2 mg/day	100 (50:50)	NA	2 weeks	TER: HM＞WM+	HM: none WM: 9 (nausea, drowsiness, abdomen discomfort)	40)
SJIT vs. Estazolam 2 mg/day	111 (63:48)	NA	4 weeks	TER: HM＞WM* Recurrence rate (6 mon f/u): HM＜WM+	NR	42)

Table 1. Continued 1

Comparison	Sample size (TG:CG)	Pattern identification	Duration	Results	Safety profiles	References
SJIT vs. Diazepam 5 mg/day	100 (50:50)	NA	2 weeks	TER: no significant difference	NR	41)
SJIT vs. Diazepam 5 mg/day	119 (60:59)	NA	4 weeks	TER: HM >WM^{+} Change of PSQI global score: HM >WM*	NR	43)
SJIT vs. Estazolam 2 mg/day	120 (63:57)	NA	3 weeks	TER: HM >WM*	HM: 2 (drowsiness, dizziness) WM: 9 (drowsiness, bitter taste in mouth, anorexia)	44)
SJIT vs. Estazolam 2 mg/day	134 (69:65)	NA	2 weeks	TER: HM >WM*	NR	45)
SJIT+Estazolam 1 mg/day vs. Estazolam 1 mg/day	114 (60:54)	liver blood deficiency pattern (肝血虧虛)	4 weeks	TER: IM >WM*	NR	46)
SJIT+Alprazolam 0.2～0.6 mg/day vs. Modified suanzaoren decoction vs. Alprazolam 0.2～0.6 mg/day	400 (260:70:70)	NA	2 weeks	TER: IM >HM, WM* PSQI -Change of sleep duration: IM >HM, WM* -Change of sleep disturbance: IM >HM, WM^{+} -Changes of sleep quality, sleep latency, sleep efficiency, daytime sleep and dysfunction: no significant difference	IM: 47 (drowsiness, dizziness, dyspepsia) HM: none WM: 34 (drowsiness, dizziness, dyspepsia)	47)
SJIT+Estazolam 1 mg/day vs. Estazolam 1 mg/day	107 (54:53)	NA	1 week	TER: IM >WM* PSQI -Sleep quality, sleep latency, sleep disturbance, and daytime dysfunction: IM <WM* -Sleep duration: IM >WM*	IM: 20 (drowsiness, dizziness, dyspepsia) WM: 20 (drowsiness, dizziness, dyspepsia)	48)
GBT vs. Estazolam 2 mg/day	110 (55:55)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	21 days	TER: HM >WM^{+} Recurrence rate (3 mon f/u): HM <WM (p-value was not presented)	NR	54)
GBT vs. Estazolam 1 mg/day	192 (96:96)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	4 weeks	TER: HM >WM* Sleep duration (assessment method was not described): HM >WM*	HM: none WM: none	55)
GBT vs. Diazepam 1 T/day	100 (50:50)	NA	NR	TER: HM >WM (p-value was not presented)	NR	56)
GBT vs. Estazolam 1 mg/day	108 (54:54)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	21 days	TER: HM >WM* Sleep duration (assessment method was not described): HM >WM*	NR	57)
GBT vs. Estazolam 1 mg/day	174 (112:62)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	10 days	TER of insomnia: no significant difference TER of accompanying symptoms: HM >WM (palpitation*, dizziness*, fatigue^{+}, nausea*, constipation^{+}) TER of EEG change: HM >WM*	HM: none WM: most of the participants experienced dizziness, fatigue, decreased response, and decreased work efficiency	58)
GBT vs. Estazolam 1 mg/day	116 (60:56)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	4 weeks	TER: HM >WM*	HM: 2 (diarrhea, gastric discomfort) WM: 7 (dizziness, poor appetite)	59)

Table 1. Continued 2

Comparison	Sample size (TG:CG)	Pattern identification	Duration	Results	Safety profiles	References
GBT vs. Estazolam 1 mg/day	100 (50:50)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	4 weeks	TER of insomnia: HM＞WM* Sleep duration (assessment method was not described): HM＞WM* TER of accompanying symptoms: HM＞WM (dizziness*, fatigue*, palpitations*, dream*)	NR	60)
GBT vs. Estazolam 1～2 mg/day	100 (50:50)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	1 month	TER: HM＞WM*	NR	61)
GBT vs. Diazepam 2.5 mg/day	100 (60:40)	NA	20 days	TER: HM＞WM*	NR	62)
GBT+Diazepam 10 mg/day vs. Diazepam 10 mg/day	100 (50:50)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	1 month	Sleep quality (the scale was not reported): IM＞WM* TER: IM＞WM *	IM: 2 WM: 21 (dizziness, diarrhea, nausea, vomiting)	63)
GBT+Diazepam 5～10 mg/day vs. Diazepam 5～10 mg/day	188 (94:94)	pattern of dual deficiency of the heart and spleen (心脾兩虛)	1 month	TER: IM＞WM* PSQI global score: HM＜WM*	IM: 2 (fatigue, gastric discomfort) WM: 15 (fatigue, drowsiness, dizziness)	64)
HBCET vs. Diazepam 5～10 mg/day	186 (96:90)	pattern of blood stasis (瘀血)	4 weeks	TER: HM＞WM* PSQI global score: HM＜WM* -Sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance,and daytime dysfunction: no significant difference Spitzer's Quality of Life Index global score: HM＞WM* -Daily life, activity, health perceptions, and behavior: HM＞WM* -Social support: no significant difference	NR	67)
HBCET vs. Diazepam 5～10 mg/day	118 (68:50)	pattern of blood stasis (瘀血)	30 days	TER: HM＞WM^{+}	NR	68)
HBCET vs. Alprazolam 0.8 mg/day	100 (50:50)	NA (refractory insomnia)	4 weeks	TER: HM＞WM*	NR	69)
HBCET vs. Diazepam 5～10 mg/day	120 (60:60)	NA (refractory insomnia)	30 days	TER: HM＞WM*	NR	70)
HBCET+Diazepam 5～10 mg/day vs. Diazepam 5～10 mg/day	100 (50:50)	pattern of internal obstruction of blood stasis (瘀血內阻)	30 days	TER: IM＞WM*	NR	71)
HBCET+Estazolam 2 mg/day vs. Estazolam 2 mg/day (for those who sleep for 4 hours each night, the dose is reduced to 1 mg; for 5 hours, the dose is reduced to 0.5 mg; 6 h, the drug can be stopped)	100 (52:48)	NA (refractory insomnia); it occurs at least 3 times a week and has lasted for at least 1 month)	60 days	TER: IM＞WM^{+} Reduction rate of estazolam dose: IM＞WM^{+}	NR	72)

CG: control group, EEG: electroencephalogram, GBT: Guibi-tang, HAMA: the Hamilton Anxiety Rating Scale, HBCET: Hyeolbuchugeo-tang, HM: herbal medicine, HMAD: the Hamilton Depression Rating Scale, IM: integrative medicine, NA: not applicable, NR: not reported, ODT: Ondam-tang, PSQI: the Pittsburgh Sleep Quality Index, SJT: Sanjoin-tang, TER: total effective rate, TG: treatment group, WM: Western medicine.

Table 2. Underlying Mechanisms of Herbal Medicines in Pre-Clinical Studies

Herbal medicine	Model	Suggested underlying mechanisms	References
ODT	Stress-induced model mouse	Anti-stress: dual-regulation of neurotransmitter levels including norepinephrine, dopamine, and serotonin in brain	13)
	Stress-induced model rats	Anti-stress: downregulation of norepinephrine and epinephrine levels in serum	12)
	Sleep-deprived rats	Improvement of negative emotions: upregulation of orexin-A and leptin expression in brain	14)
SJIT	Elevated plus-maze model rats	Anxiolytic: upregulation of GABA/GLU ratio	27)
	PCPA-induced insomnia rats	Sleep induction: downregulation of GLU and GABA, and upregulation of GLU/GABA ratio, 5-HTP, and 5-HIAA in brain	26)
	PCPA-induced insomnia rats	Sleep induction: upregulation of ATP level in frontal cortex	73)
	PCPA-induced insomnia rats	Sleep induction: downregulation of GFAP and P2X7R expression in cerebral cortex	31)
	PCPA-induced insomnia rats	Sleep induction: downregulation of mGluR1 and mGluR2 expression in cerebral cortex	32)
	PCPA-induced insomnia rats	Sleep induction, neuroprotective: upregulation of glucose level and downregulation of lactate, glycerol, and glutamate in cerebral cortex	29)
	D-galactose and MMPM-induced elderly insomnia rats	Sleep induction, neuroprotective: downregulation of GLU and GABA in cortex and hypothalamus, downregulation of GABAAR α1 and γ2 expressions in cortex and hippocampus, and downregulation of GABAAR α1 and γ2 mRNA expressions in cortex	28)
	MPWE-induced chronically sleep-deprived elderly rats	Sleep induction: downregulation of GABA protein expression in hypothalamus, and downregulation of GABAAR α1 and GABAAR γ2 mRNA expressions in hypothalamus	30)
	MPWE-induced chronically sleep-deprived elderly rats	Regulation of circadian rhythm: downregulation of c-Fos and nNOS protein and mRNA expressions in hypothalamus SCN	33)
	MPWE-induced chronically sleep-deprived rats	Regulation of circadian rhythm: downregulation of TL, TD, and TALL, and upregulation of Clock and Bmal1 protein expression in SCN	34)
	MPWE-induced chronically sleep-deprived elderly rats	Regulation of circadian rhythm: upregulation of VIP protein and mRNA expression in SCN, down regulation of AVP protein expression in SCN, and upregulation of AVP mRNA expression in SCN	35)
	MPWE-induced chronically sleep-deprived elderly rats	Inhibition of cardiomyocyte apoptosis: downregulation of Bcl-2 and Bax expressions, and Bax/Bcl-2 ratio in cardiomyocyte, downregulation of apoptosis index (%)	36)
	MK-801-induced hippocampus injury mouse	Anti-depression: upregulation of ERK2, CaMK II, CREB phosphorylation	37)
GBT	Immobilization stress mice	Anti-stress: downregulation of serotonin levels in frontal cortex, hypothalamus, and striatum	51)
	Immobilization stress mice	Anti-stress: downregulation of epinephrine, norepinephrine, and dopamine in brain	50)
	Immobilization stress mice	Anti-stress: downregulation of histamine and corticosterone levels in serum	53)
	Immobilization stress mice	Anti-stress: downregulation of histamine and corticosterone levels in serum	52)
	Healthy mice	Sedative effect: prolongation of pentobarbital-induced sleeping time and inhibition of GABA transaminase activity in brain	49)
HBCET	Immobilization stress mice	Anti-stress: downregulation of dopa decarboxylase and tyrosine hydroxylase expression, and upregulation of monoamine oxidase expression in brain	66)

5-HIAA: 5-hydroxyindoleacetic acid, 5-HTP: 5-hydroxytryptophan, ATP: adenosine triphosphate, AVP: arginine vasopressin, CaMK: Ca2+/calmodulin-dependent protein kinase, CREB: cAMP-response element binding protein, ERK: extracellular signal-regulated kinase, GABA: γ-aminobutyric acid, GABAAR: γ-aminobutyric acid type A receptor, GBT: Guibi-tang, GFAP: glial fibrillary acidic protein, GLU: glutamate, HBCET: Hyeolbuchugeo-tang, MMPM: modified multiple platform method, nNOS: neuronal nitric oxide synthase, ODT: Ondam-tang, PCPA: p-Chlorophenylalanine, SCN: suprachiasmatic nucleus, SJIT: Sanjoin-tang, VIP: vasoactive intestinal polypeptide.

in the herbal medicine group, such as fatigue, dry mouth, nausea, and heartburn (9/410, 2.20%), was lower than that in the WM group, which experienced events such as drowsiness, dry mouth, dizziness, and anorexia (73/389, 18.77%) (Table 1).

There were two large-scale RCTs comparing *Ondam-tang* combined with WM versus WM alone[24,25]. The WMs used in both studies were estazolam or paroxetine. Both studies recruited participants with patterns of internal harassment of phlegm-heat (痰熱內擾). Treatment periods were 2 weeks or 4 weeks. Li (2015)[24] reported that the integrative medicine (IM) group showed significantly higher TER than the WM group. There was no AE reported in either group. Wen (2014)[25] reported that the IM group showed significantly higher TER and lower global score, sleep latency, sleep duration, sleep efficiency, sleep disturbance, daytime dysfunction of PSQI, Hamilton

Anxiety Rating Scale (HAMA) score, and Hamilton Depression Rating Scale (HAMD) score than did the WM group. They did not report the safety profiles related to the interventions (Table 1).

2. *Sanjoin-tang*

1) Preclinical evidence

According to some preclinical studies, *Sanjoin-tang* mainly exerted anxiolytic and sleep induction effects through regulation of neurotransmitter levels, such as glutamate and γ-aminobutyric acid (GABA)[26-30], their receptors, such as GABA type A receptors (GABAARs)[28,30]; some of their metabolites, such as 5-hydroxytryptophan (5-HTP) and 5-hydroxyindoleacetic acid (5-HIAA); purine receptor (P2X7 receptors, P2X7R)[31]; glial fibrillary acidic protein (GFAP); and metabotropic glutamate receptors[32]. Moreover, *Sanjoin-tang* regulates the circadian rhythm by regulating the mRNA and protein expression of c-Fos, neuronal nitric oxide synthase (nNOS)[33], Clock, Bmal1[34], vasoactive intestinal polypeptide (VIP), and arginine vasopressin (AVP)[35], in the suprachiasmatic nucleus. In addition, *Sanjoin-tang* was effective in inhibiting cardiomyocyte apoptosis in a chronically sleep-deprived rat model[36], and in improving depressive behavior in a mouse model of hippocampus injury (Table 2)[37].

2) Clinical evidence

There were eight large-scale RCTs comparing *Sanjoin-tang* and WM[38-45]. All WMs used were benzodiazepines, including diazepam and estazolam. None of these studies recruited participants with specific pattern identification. All treatment periods were 2~4 weeks, and the most frequently used outcome was TER[38-45]. Except for one study that reported no significant difference[41], *Sanjoin-tang* showed significantly better results on TER than WM in all other studies (7/8, 87.5%)[38-40,42-45]. In two studies (2/8, 25%)[38,39], where the Spiegel scale score was reported as the primary outcome, the *Sanjoin-tang*-treated group showed significantly higher scores than the WM group in both studies. One study reported the change in the PSQI global score as the outcome, and the *Sanjoin-tang* group showed significantly higher improvement than the WM group[43]. In one study that reported recurrence rate at the 6-month follow-up as the primary outcome, the recurrence rate was lower in the *Sanjoin-tang* group (14/59, 23.73% vs. 32/39, 82.05%; $p<0.01$)[42]. Two studies (2/8, 25%) reported AEs[40,44], and the incidence of AEs in the herbal medicine group (2/113, 1.77%; such as drowsiness and dizziness) were less than in the WM group (18/107, 16.82%; such as nausea, drowsiness, abdominal discomfort, and bitter taste in the mouth) in both studies (Table 1).

There were three large-scale RCTs comparing *Sanjoin-tang* combined with WM and WM alone[46-48]. The WMs used in the studies were estazolam and alprazolam. Treatment periods were 1[48], 2[47], and 4 weeks[46], respectively. Long (2013)[46], which recruited participants with liver blood deficiency pattern (肝血虧虛), reported that the IM group showed significantly higher TER than WM group. Wu (2008)[47] compared the herbal medicine, WM, and IM groups, and reported that the IM group showed the highest TER. The study also reported PSQI as their outcome, and improvements in sleep duration and sleep disturbance were significantly better in the IM group than in the other two groups. There were no significant differences in changes in sleep quality, sleep latency, sleep efficiency, daytime sleep, and dysfunction between the groups. There were no AEs in the herbal medicine group, but the WM group (34/70, 48.57%) and IM group (47/260, 18.08%) showed some mild to moderate AEs, including drowsiness, dizziness, and dyspepsia. Yang (2015)[48] reported that the

IM group showed significantly higher TER than the WM group. The study also reported PSQI as their outcome, and sleep quality, sleep latency, sleep disturbance, and daytime dysfunction were significantly lower in the IM group, while sleep duration was significantly higher in the IM group than in the WM group. The occurrence and symptoms of AEs in the IM group (20/54, 37.04%; such as drowsiness, dizziness, and dyspepsia) and WM group (20/53, 37.74%; such as drowsiness, dizziness, and dyspepsia) were similar (Table 1).

3. *Guibi-tang*

1) Preclinical evidence

According to a pre-clinical study, *Guibi-tang* exerted sedative effects by inhibiting GABA transaminase activity in the brain of healthy mice[49]. In addition, *Guibi-tang* has shown anti-stress effects by modulating neurotransmitter levels, such as epinephrine, norepinephrine, and dopamine, in the brain[50,51], and histamine and corticosterone in the serum of immobilization stress-induced mouse models (Table 2)[52,53].

2) Clinical evidence

There were nine large-scale RCTs comparing *Guibi-tang* and WM[54-62]. The WMs used in all these studies were benzodiazepines, including diazepam and estazolam. Most of these studies (7/9, 77.78%)[54,55,57-61] recruited participants with specific pattern identification of dual deficiency of the heart and spleen (心脾兩虛). Except for one study that did not specify the treatment duration[56], all treatment periods were 10 days to 4 weeks. The most frequently used outcome was TER[54-62]. Except for one study that reported no significant difference[58], *Guibi-tang* showed significantly better results on TER than WM in all other studies (8/9, 88.89%)[54-57,59-62]. In three studies (3/9, 33.33%)[55,57,60], where the total sleep time (assessment method was not described) was reported as the outcome, the *Guibi-tang* group showed significantly longer sleep times than the WM group. One study reported recurrence rate at the 3-month follow-up, and there was no significant difference between the groups (9/50, 18% vs. 17/47, 36.17%; p-value was not presented)[54]. Three studies (3/9, 33.33%) reported AEs. In one study, AEs did not occur in either group[55]. In another study, AEs occurred only in the WM group (the number of incidences was not specified)[58]. In the remaining study, the incidence of AEs was lower in the herbal medicine group (2/60, 3.33%; AEs such as diarrhea and gastric discomfort) than in the WM group (7/56, 12.5%; AEs such as dizziness and poor appetite) (Table 1).

There were two large-scale RCTs comparing *Guibi-tang* combined with WM versus WM alone[63,64]. Both studies used diazepam as the WM, and the treatment period was 1 month in both cases. Both studies recruited participants with a pattern of dual deficiency of the heart and spleen (心脾兩虛), evaluated TER and sleep quality, and reported significantly favorable results on these outcomes in the IM groups. Moreover, the IM groups (4/144, 2.78%; such as fatigue and gastric discomfort) showed fewer AEs than the WM groups (36/144, 25%; such as dizziness, diarrhea, nausea, and vomiting) (Table 1).

3) Herb-drug interaction

A study by Korean researchers found that when repeatedly administered *Guibi-tang* orally, the mRNA expression of CYP1A2 or 2B1/2 significantly increased in Sprague Dawley rats; therefore, caution should be taken when concomitantly administering *Guibi-tang* and WM metabolized by the enzymes[65].

4. *Hyeolbuchugeo-tang*

1) Preclinical evidence

According to a preclinical study[66], *Hyeolbuchugeo-tang* showed anti-stress effects by downregulating the expression of dopa decarboxylase and tyrosine hydroxylase, and upregulating the expression of monoamine oxidase in the brains of immobilization stress-induced mouse models (Table 2).

2) Clinical evidence

There were four large-scale RCTs comparing *Hyeolbuchugeo-tang* and WM[67-70]. All WMs used in these studies were benzodiazepines, including diazepam and alprazolam. Half of these studies recruited participants with specific pattern identification of patterns of blood stasis (瘀血)[67,68], while the other two studies recruited participants with refractory insomnia[69,70]. All treatment periods were 4 or 30 days. The most frequently used outcome was TER[67-70], and *Hyeolbuchugeo-tang* showed significantly better results on TER than WM in all studies. A study reported PSQI and Spitzer index as their outcome, and the global score of PSQI in the herbal medicine group was significantly lower than that in the WM group, while there were no significant differences in its subscales, including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, and daytime dysfunction, between the groups[67]. In the case of the Spitzer index, the global score and subscales, including daily life, activity, health perceptions, and behavior were significantly higher in the herbal medicine group, while the subscale social support showed no significant difference[67]. No studies reported the safety profile of the interventions used (Table 1).

There were two large-scale RCTs comparing *Hyeolbuchugeo-tang* combined with WM and WM alone[71,72]. The WMs used in the studies were diazepam[71] and estazolam[72]. Treatment periods were 30 days[71] and 60 days[72], respectively. Wang (2014)[71], who recruited participants with patterns of internal obstruction of blood stasis (瘀血內阻), reported that the IM group showed significantly higher TER than the WM group. Yang (2011)[72], who recruited participants with refractory insomnia, also reported that the IM group showed a significantly higher TER than the WM group. Moreover, the dose reduction rate of estazolam was significantly higher in the IM group. Neither study reported the safety profile of the interventions used (Table 1).

IV. DISCUSSION

1. Summary of findings

Four herbal medicines (*Ondam-tang, Sanjoin-tang, Guibi-tang*, and *Hyeolbuchugeo-tang*) were reviewed in this mini-review. Although there was no evidence to support the use of herbal medicine in the treatment of insomnia in patients with COVID-19, it is worth reviewing articles investigating herbal medicines used for primary insomnia to provide evidence regarding its benefits to patients and general population.

According to the included studies[15-25,38-48,54-64,67-72], herbal medicines were used as monotherapies or add-on interventions in clinical trials of primary insomnia. The duration of treatment ranged from 1 to 60 days. Most of the results favored herbal medicine monotherapy or integrative therapy, which is a combination of herbal medicine and WM, on TER of insomnia, except for three studies[21,41,58]. In 13 RCTs that reported safety profiles[15-18,20,21,24,40,44,47,55,58,59], 13 cases (1.41%) out of 921 participants in the herbal medicine groups reported AEs, including fatigue, drowsiness, dizziness, dry mouth/bitter taste in the mouth, nausea, diarrhea, gastric discomfort, heart-

burn, or hyperhidrosis, *versus* more than 132 cases (>15.68%) of 842 participants in the WM group reported AEs, including fatigue, drowsiness, dizziness, dry mouth/bitter taste in mouth, nausea, gastric discomfort, or poor appetite. In five RCTs that reported safety profiles[24,47,48,63,64], 71 cases (13.71%) of 518 participants in the IM group reported AEs, compared to 90 cases (27.52%) of 327 participants in the WM group. Preclinical studies found that the potential mechanisms of herbal medicines on sleep improvement include anti-stress effects via regulation of neurotransmitters, anxiolytic effects, sedative effects, effects on negative emotions, and sleep-inducing effects[12-14,26-37,49-53,66,73].

2. Suggestions of herbal medicines for insomnia in the COVID-19 era

The role of herbal medicine during the COVID-19 era is emerging. The reasons for this may include limitations of conventional medicine, such as unsatisfactory clinical outcomes of management strategies using only conventional medicine[74], while accumulating clinical evidence supports the use of supplemental herbal medicine may improve the clinical outcomes of COVID-19 patients[75]. In addition, since herbal medicines have multiple properties in addition to antiviral effects against SARS-CoV-2, other clinically useful effects such as anti-inflammatory, immune enhancement, and vitality enhancement can be expected[76]. Among them, the improvement of mental health is a major expected effect, and evidence-based approaches to herbal medicine have already been proposed for various psychiatric diseases, such as depression, insomnia, and anxiety disorder[77].

In this literature review, the herbal medicines suggested in the KM clinical practice guidelines for insomnia (version 1.0) were considered as the herbal medicines of interest, including *Ondam-tang*, *Sanjoin-tang, Guibi-tang,* and *Hyeolbuchugeo-tang*. Although there are not enough data to make a firm clinical distinction between these herbal medicines, we would like to provide the following suggestions for the use of herbal medicines for insomnia for future use at the COVID-19 telemedicine center of KM, based on existing clinical and preclinical evidence. (1) *Ondam-tang*: This herbal medicine has been reported to have anti-stress and mood-improving effects from preclinical studies, and clinical evidence may show a specific effect in treating primary insomnia related to phlegm (痰). According to a previously published systematic review[78], patients with primary insomnia related to pathological phlegm (痰) may exhibit the following symptoms: insomnia, restless sleep, dizziness, vexation, bitter taste, profuse sputum, oppression in the chest, gastric stuffiness, heavy headedness, acid regurgitation, poor appetite, belching, headache, and nausea. These symptoms are mainly associated with problems of the digestive system and can be interpreted as part of the stress response seen in insomnia patients. (2) *Sanjoin-tang*: This herbal medicine is well known for treating insomnia. In addition to this herbal medicine, the hypnotic-sedative effect of *Semen Ziziphi Spinosae*, the main constituent herb, has been reported in a number of studies[79]. According to our literature review, this herbal medicine showed little association with specific pattern identification. Therefore, this may be considered generally for its anxiolytic and sleep-inducing effects in patients with primary insomnia. (3) *Guibi-tang*: This herbal medicine has been reported to have anti-stress and sedative effects from preclinical studies. According to our literature review, the pattern of dual deficiency of the heart and spleen (心脾兩虛) was set as the main target in clinical studies using this herbal medicine in patients with insomnia patients. According to a previously published systematic review[78], patients with primary insomnia related to this pattern may exhibit the following symptoms: ex-

cessive dreaming, difficulty staying asleep, difficulty falling asleep, insomnia, light sleep, palpitation, lassitude, worse complexion, poor memory, dizziness, fatigue, loss of taste, weary limbs, poor appetite, and sloppy stool. These symptoms can be generally interpreted as decreased vitality and not being able to easily achieve a state of relaxation. (4) *Hyeolbuchugeotang*: This herbal medicine is a representative prescription to treat blood stasis. Blood stasis is largely related to chronic internal diseases and external injuries[80], and diseases related to this pattern are usually recognized as chronic or refractory. According to the results of the literature review, the pattern of blood stasis (瘀血) and refractory insomnia were set as the main targets in clinical studies using this herbal medicine in patients with insomnia. Attempts are currently being made to establish the pathology of blood stasis (瘀血)[81]. In addition to classic symptoms such as a history of traumatic injury, abnormal blood circulation, and pain in fixed areas, refractory insomnia may be a condition where this herbal medicine should be considered.

3. Strengths and limitations

This study provides information that can have implications on the use of herbal medicine to treat insomnia in a situation where mental health was increasingly becoming important. In addition, our literature review results could be considered in the future to broaden therapeutic options for herbal medicine in treating patients with insomnia at the COVID-19 telemedicine center of KM.

However, the following limitations should be considered in the interpretation of this study. First, since this review does not take the form of a systematic review, it may have a potentially biased scope. In particular, this study did not review all available herbal medicines for primary insomnia, but literature searches were conducted on herbal medicine suggested in the KM clinical practice guidelines for insomnia (version 1.0). In other words, this limitation of scope suggests that the results of this review may have clinical relevance in the Korean medical system, but not in other countries. Second, in this review, preclinical studies were collected to explore the underlying mechanisms of the candidate herbal medicines for insomnia, but the results of preclinical studies cannot be directly translated into human subjects. Therefore, the results obtained in preclinical studies have meaning as presumptive data to explore the underlying mechanism. Finally, herb-drug interactions are regarded as an important issue in the use of herbal medicine, but our literature review included only one herb-drug interaction study[65]. In order to consider herbal medicine as a supplement to WMs in the future, further interaction studies are urgently needed.

V. CONCLUSIONS

In this mini-review, the authors summarized the evidence of some promising herbal medicines available for primary insomnia, based on existing clinical and preclinical studies. Based on these findings, some suggestions of herbal medicines for insomnia in the COVID-19 era in Korea were suggested. These data may be useful for future revision of the manual of COVID-19 telemedicine center of KM.

CONFLICT OF INTEREST

None.

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