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Stress-, Anxiety-, and Cellphone use-induced Sleep Deficits and Psychological Conditions during the Pandemic and a Potential Remedy: a Randomized, Parallel, Blinded, Placebo-controlled Study

EDITORIAL

Healthier environments could prevent almost one quarter of the global burden of disease. The COVID-19 pandemic is a further reminder of the delicate relationship between people and our planet (WHO 2022). Since the appearance of the cell phone, the anomalous use of this device has called into question, as a new healthier environment issue, especially during this COVID-19 virus pandemic spreading, which may be linked to social isolation. This problem is identical to the one regarding the existence of behavioral addictions, including rigidity and muscle pain, ocular afflictions resulting from Computer Vision Syndrome reflected in fatigue, dryness, blurry vision, irritation, or ocular redness, auditory and tactile illusions – the sensation of having heard a ring or felt a vibration of a cell phone, and pain and weakness in the thumbs and wrists leading to an increased number of cases of de Quervain's tenosynovitis. With respect to the psychological problems derived from cellphone dependence, the research focuses on the sub-consequence of cellphone dependence, sleep interference and its coexistence with using substances such as alcohol and tobacco and with symptomatology and psychiatric comorbidities, particularly anxiety, stress, and depression. In this study, authors surveyed 288 volunteers to gain insight regarding how stress, anxiety, and time spent on cellphones affected sleep and mood, and how a novel herb compound preparation, dihydromyricetin (DHM)-containing product improves these syndromes. The results clearly showed a negative linear correlation between sleep duration vs stress level and time on cellphone, and a negative correlation between wake-up mood/symptoms vs stress. Interestingly, volunteers taking DHM-containing product, but not placebo, showed substantial improvements in stress levels, hours of sleep, especially cellphone dependence, and wake-up mood/symptoms.

This is a very interesting study warns us that social isolation is how harmful for our health. Anxiety is likely to have long-term effects, secondary to irreversible neuro-dysfunction. In another hands, DHM showed that it can be a potential remedy for improving anxiety. This study addresses current health concerns and new health contexts and proposes a potential remedy role for DHM and/or herbal medicines in behavioral addictions and related mental health and well-being.

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ORIGINAL ARTICLE

Stress-, Anxiety-, and Cellphone use-induced Sleep Deficits and Psychological Conditions during the Pandemic and a Potential Remedy: a Randomized, Parallel, Blinded, Placebo-controlled Study

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ABSTRACT

Background: **Coronavirus disease-19 (COVID-19) and its unprecedented disruption of daily life has resulted in increased anxiety, stress, and cellphone dependence as a means of societal connection. More individuals substantially suffer disruptions in their sleep, likely connected to the pandemic's social isolation and related stress, anxiety, and increased screen time.**

Objectives: **To gain insight into how stress, anxiety, and time spent on cellphones affected sleep and mood during the time of COVID-19 pandemic and social isolation, and to evaluate the efficacy of dihydromyricetin (DHM) on improving these conditions.**

Methods: **Men and women aged 18-60 were randomly assigned to the interventional DHM group (n=250) or placebo group (n=194). Participants self-administered treatment (DHM or placebo) for 20 consecutive days. Surveys were sent to and completed by the participants the day before the 20-day treatment start date and the day following treatment end date. The primary outcome measures were effect of DHM on sleep duration, stress levels, cellphone time, and feelings after waking up. Retrospectively registered 25 July 2021 - https://clinicaltrials.gov/ct2/show/NCT05280561**

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Results: **We found 1) a negative linear correlation between sleep duration vs stress level and time on cellphone, 2) a negative correlation between wake-up mood/symptoms vs stress, and that 3) volunteers taking DHM showed substantial improvements in stress levels, hours of sleep, cellphone dependence, and wake-up mood/symptoms as compared to taking placebo.**

Conclusions: **Overall, this work illustrates the value of DHM as an alternative remedy for improving mental health and wellbeing in conditions such as social isolation and stress.** (*Int J Biomed Sci* 2022; 18 (3): 42-53)

Keywords: anxiety; stress; sleep; dihydromyricetin; isolation; survey; COVID-19; pandemic

INTRODUCTION

The rapid spread of the novel coronavirus disease (COVID-19) has resulted in a disruption of businesses, immense number of unexpected deaths, and disruption of billions of lives throughout the world with the consequence of a major downturn on economies (1-3). These substantial consequences have resulted in heightened stress and anxiety linked to health issues, employment disruptions, and financial hardships, all of which have been exacerbated with social isolation mandates (4-7). Interestingly, a second consequence of the pandemic was a significant increase in cellphone and social media usage as a means of communication and companionship (8-10). It is not hard to understand or envision how these increased levels of stress, anxiety, worry, and reliance on cellphones could result in detrimental changes to physical and psychological wellbeing. In fact, there is growing realization that a serious impact of increased screen time and declined mental wellbeing is a disruption in sleep patterns and rhythms (11-13). Approximately one third of our lives are spent sleeping, and disruptions in adequate and restful sleep can adversely affect health and mental fitness (14). Understanding how the relationships between stress, anxiety, sleep, and psychological problems affect daily life is an unmet need where further investigations are needed.

Anxiety is a negative emotional state characterized by feelings of worry and apprehension, and is accompanied by specific somatic, cognitive, and behavioral manifestations (15, 16). Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nerve system (CNS), plays an important role in the modulation of anxiety responses and sleep in both normal and pathological states (17). When we sleep, our eyes close, breathing slows, and muscles and mind gradually relax due to the effects of GABA (18). The GABAergic (i.e. pertaining to or affecting GABA) neurons in the brain switch to a sleeping state, beginning the innumerable biological processes that refresh our body and mind (17). Sleep supports nearly every system in the body (19), and the rejuvenation provided by sleep is vital for our cardiovascular and immune systems, as well as our ability to think clearly, learn new information, and manage emotions (20).

Three stages of sleep are commonly descripted (21). The first stage is relaxation, which is the transition from wakefulness to sleep. The second stage of sleep is a period of sleep onset. The third stage of sleep is the period of deep sleep that people need to feel refreshed in the morning (21). GABAergic neurotransmitters and potentiation of $GABA_A$ receptors ($GABA_A$Rs) play an essential role in sleep initiation and maintenance (18, 22). Thus, a common therapeutic avenue for sleep problems is $GABA_AR$ potentiation through agonists like benzodiazepines (BZs) (23). However, there are many accompanying issues with BZ usage, such as the risk of addiction, tolerance, and feeling groggy in the morning due to forceful sleep, among others (24).

Our group has systemically developed dihydromyricetin [(2R,3R)-3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydrochromen-4-one] (DHM) extracted from *Hovenia* and *Rattan* (25-30). We identified that DHM is a positive allosteric modulator (PAM) of $GABA_A$Rs that can counteract anxiety and depression with at least a portion of these outcomes via activity on $GABA_AR$ (26, 27, 29). In rodents, DHM positively modulated $GABA_AR$ without inducing tolerance, and reduced inflammation and oxidative stress induced by alcohol intoxication, alcohol withdrawal, as well as social isolation-induced anxiety (26, 28, 29, 31). Behaviorally, DHM-administered transgenic Alzheimer's disease (AD) and socially isolated mice showed improve-

ments in anxiety-related behaviors as well as cognitive abilities (25, 29, 31, 32). A 2017 review by Li *et al*. explained the versatile beneficial effects of DHM with minimal adverse effects, ranging from antioxidative and anti-inflammatory properties to regulation of lipid and glucose metabolism (33). Further, we have been extensively investigating the benefits of botanicas and herbs as an alternative to prescription drugs, where we found that a variety of flavonoid extracts can relieve stress and anxiety (29, 30). Combined, DHM has the potential to be further developed as a method for reducing stress and improving $GABA_AR$-related functions, including sleep.

Over the past two years, growing evidence has revealed that COVID-19 has varying detrimental effects on individuals, with many suffering from anxiety, stress, nervousness, and difficulty sleeping (4, 34-37). Thus, we questioned whether there is any relationship(s) between stress levels, quality of sleep, cellphone use, and overall wellbeing. To address this question, we developed a survey which we made available via an online link. This survey was undertaken to identify and group individuals that were suffering from stress and anxiety as well as to investigate the related stressors during the pandemic. We then introduced DHM to those who were voluntarily willing to evaluate its effects on alleviating stress and improving sleep quality. The goal of our work was to explore if DHM plays a pivotal role in enhancing and/or accelerating the three stages of sleep, including relaxation → sedation → and restful sleep, assessed via self-reported surveys.

MATERIALS AND METHODS

Survey form

The studies were reviewed and approved by the University of Southern California Institutional Review Board (IRB Record ID: UP-21-00653). The participants provided their written informed consent to participate in this study. This study adheres to CONSORT guidelines.

We sent out the first questionnaire (20 participants) through email systems of companies and colleges to examine the participants' major stressors during the COVID-19 pandemic, amount of sleep, and feelings after waking up over the past three months. Our initial survey helped us identify and classify stressors. This survey was then optimized into the final version to assess the changes in sleep and emotional states in a larger group of participants. The participants who were voluntarily willing to evaluate effects on alleviating stress and improving sleep quality were randomly and blindly assigned to DHM or placebo group.

Stress is defined as the physical or psychological response to an external cause in which the demands of a situation (such as problems from work, family, friends, health, finance or the environment) threaten to exceed the resources of the individual in a way that affects the individual's emotional state or ability to carry out daily tasks (38-40). As such, we summarized common stressors and classified stress levels into eight categories (Table 1).

Within the stressors in the survey, 'Work/career' means the harmful physical and emotional responses that occur when the requirements of the job do not match the capabilities, resources, or needs of the worker (39). 'Relationship' refers to the associations, interactions, and bonds between two or more people. 'Environment' refers to anything that surrounds a person, including physical, chemical, and other natural living things. 'Memory from childhood' refers to memories formed during childhood (41, 42). In this survey, 'memory' was directed at negative or emotional memories such as the loss of a family member or a past traumatic event. 'Bad experience' refers to experiences such as violence, abuse, or unforgettable failures. 'Health issue(s)' means feelings of powerlessness or weakness. Anyone diagnosed with disease(s) (see "The volunteer participants" section) were not included in this survey study.

To quantify stress counts and severity, a 'Yes' counted as 1 point, a 'No' counted as 0 points, and a 'Not sure' counted as 0.5 points. The higher the score, the greater the severity of stress. All causes of stress were counted as independent factors that affect sleep time (43). Hours of sleep were calculated as follows: actual hours of sleep = bedtime – time trying to sleep. The online survey was created on Google forms by our team member: https://forms.gle/cZGR9iVsG4Aninwf8

To assess the participant's sleep and psychological status, in addition to stress and time spent on cellphones, we asked detailed questions about how they felt after waking up. Within 'Survey', the state of being asleep considers getting into bed, preparing to sleep, and how many hours they are actually asleep. We asked whether the participant dreamed during sleep. Additionally, some people wake up in the middle of the night. If the period of wakefulness is short and they go back to sleep quickly, we counted the sleep as continuous. Based on common complaints, we listed the most typical uncomfortable sleep-related symptoms, such as tiredness, headache, loss of strength, inability to focus on tasks, irritability, or feelings of disinterest, hopelessness, purposelessness, worry, and depression.

Table 1. Survey

What is today's date?	__ __/__ __/__ __ (mm/dd/yyyy)
How would you describe your stress level?	[ ] Mild [ ] Moderate [ ] Severe [ ] None (*no stress)*
If your level of stress was "Mild", "Moderate", or "Severe", please indicate the possible causes of the stress:	Check *ALL* that apply: [ ] N/A (check if "*None*" is marked for Question # 8 for stress level indication) [ ] Work/career [ ] School/study [ ] Relationships (e.g., friends, family, partner, co-workers) [ ] Financial problems [ ] Environment (e.g., noise, air quality, light, natural or man made disasters) [ ] Life changes/events (e.g., divorce, death, wedding, moving, having a child) [ ] Daily life and busyness [ ] Health (physical/mental illness) [ ] Self-induced (e.g., perfectionism, self-pressure, suicidal thoughts, competitive) [ ] Poor diet/nutrition (e.g., caffeine, processed foods, refined sugars) [ ] Traumatic event exposure or experience [ ] Social isolation
On average, how long (in hours) do you spend on your cellphone?	__ __ hours
On average, how long (in minutes) does it take you to fall asleep?	__ __ minutes
On average, how long (in hours) do you sleep daily?	__ __ hours
On average, do you dream when you sleep?	[ ] Yes [ ] No
On average, how do you feel after waking up?	Check *ALL* that apply: [ ] Refreshed [ ] Fatigue (feel of tiredness and/or lack of energy) [ ] Heart racing [ ] Dizzy or lightheaded [ ] Sleepy [ ] Headache [ ] Nauseous [ ] Irritable/angry [ ] Unhappy [ ] Difficulty concentrating [ ] Hopeless/desperate [ ] Lack of motivation [ ] Depressed [ ] Slow/sluggish response [ ] Internal pressure [ ] Restlessness [ ] Tense [ ] Anxious [ ] Nervous [ ] Worry [ ] Fearful [ ] Emotional [ ] Thoughts of hurting yourself or others [ ] No purpose in life

The volunteer participants

The survey was collected from participants aged 18 to 60, both males (49%) and females (51%) in Chengdu and Beijing, China (Table 1). Participants selected a number, 1 or 2, and were allocated to the corresponding treatment (1 for DHM and 2 for placebo). Participants were blinded to the treatment corresponding to each number. Education levels of all participants were above high school. The participants worked in companies or were graduate students. The final data was selected from those who were able and willing to sign informed consent, between the ages of 18 to 60 at the time of consent, and had no alcohol or drug use, chronic (diagnosed) illnesses, COVID-19 infection, or current use of prescription medication, including antidepressants, at the time of consent. Exclusion criteria also included pregnant or breastfeeding women, use of current sleep prescriptions, report of napping at least three times per week, and history of sleep apnea. Medical history was self-reported. Recruitment began on October 1, 2020, and closed on March 31, 2021, on a rolling enrollment led by one of our team members. The sample size was based on a prior power analysis using G-Power 3, for a Mixed Model Repeated Measures Analysis of Variance (MMRMA) design, assuming a statistical power of 0.8, moderate effects of the DHM effects on sleep outcomes, and hypothesis tests conducted at a probability value of 0.05. Participants were instructed to take placebo or DHM daily at the same time each day. Treatment was self-administered once daily for 20 days with no crossovers and followed up with the post-survey the day following the end of the 20-day treatment. Overall, 64.3 % of 444 respondents completed the study (Fig. 1). Table 2 shows the baseline demographics and clinical characteristics for the DHM and placebo group.

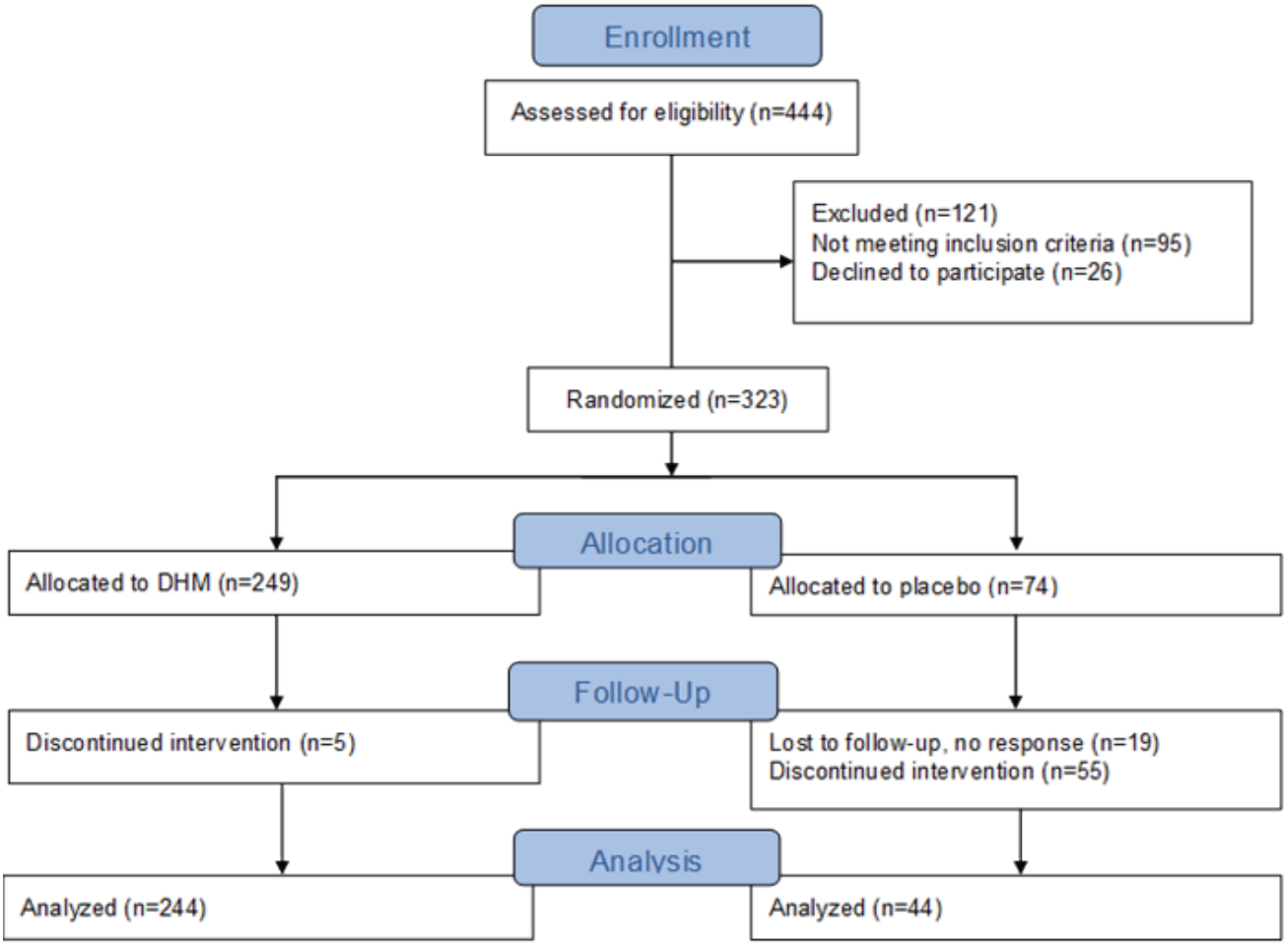

Figure 1. CONSORT flow diagram.

Table 2. Baseline demographics and clinical characteristics for each group

	DHM	Placebo	Total
Mean age (yrs)	38 ± 9	33 ± 8	
Age range	18-60	20-55	
Median	40	33	
N	244	44	288
Gender	N (%)	N (%)	
Male	125 (51)	21 (49)	146
Female	119 (49)	23 (51)	142
Race	N (%)	N (%)	
Asian	244 (100%)	44 (100%)	288

Treatment preparation

The placebo contained excipients including extracts of celery, strawberry, oranges, rose, and beet blended in powder form of 1 g. The DHM formula contained DHM 200 mg (HPLC purified ≥ 98%, Master Herbs Inc., Pomona, CA) plus same excipients as placebo. 2 g of the powder were dissolved in ~100 ml water for oral self-administration.

Statistical Analyses

The effects of DHM/placebo were analyzed with two-way ANOVA followed by multiple comparison (Holm-Sidak method). $p \leq 0.05$ was considered statistically significant. Correlations among variables were analyzed with multiple regression using proc GLM SAS 9.4. A general linear model with interactions was used:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3 + b_7X_1X_2X_3 + \varepsilon \quad 1)$$

The p value of regression coefficients (the slopes of the regression lines) of ≤ 0.05 was considered to be a significant correlation.

RESULTS

Correlations of sleep duration vs stress levels and cellphone time: DHM improves stress levels and sleep duration

During the pandemic, we hypothesize that many people were experiencing increased stress levels, partially due to social isolation. As an outcome of the isolation, cellphone usage and screentime increased, where social media became an outlet for societal connection (9, 10). Unfortunately, this increased use of cellphones could have unhealthy consequences such as reduction in quality sleep time (12, 13). As presented in Fig. 2A and Fig. 2B, we found negative linear correlations of sleep duration versus (vs) stress level and vs time spent on cellphone. Moreover, we found that cellphone usage was positively correlated with stress levels (Fig. 2C). There was no significant interaction between stress levels and cellphone usage on sleep duration.

On the other hand, individuals taking DHM for 20 days reported that their stress levels were reduced from score 2.86 ± 0.103 to 1.25 ± 0.13 (Fig. 2G) and the stress levels in most of the participants were 3 or less (Fig. 2A). In addition, these individuals reported that their sleep duration increased from 5.45 ± 0.113 to 6.52 ± 0.143 h (Fig. 2H and Fig. 2A). DHM also reduced their time spent on cellphone from 3.12 ± 0.099 to 2.27 ± 0.124 h (Fig. 2I), as illustrated by the fact that the majority of the participants spent 4 hours or less on their cellphones (Fig. 2B and Fig. 2C).

Our multiple regression result:

$$Y_1 = 9.15 - 0.76X_1 - 0.41X_2 - 0.87X_3 - 0.048X_1X_2 + 0.23X_1X_3 + 0.017X_2X_3 + 0.026X_1X_2X_3 \quad 2)$$

Y_1 is the sleep duration and b_is are regression coefficients. X_1 denotes the categorical variable before or after DHM administration. X_2 denotes stress levels, and X_3 denotes cellphone usage.

We found significant negative linear correlations of sleep duration vs stress level and vs cellphone usage before and after DHM treatment (Fig. 2A, 2B). Also, the time the participants spent on their cellphones was positively correlated with stress levels before and after DHM (Fig. 2C). There is also an interaction between DHM administration and cellphone use on sleep duration (Fig. 2B), indicating that the effect of cellphone usage on sleep duration is reduced by DHM.

We performed the same analyses for the placebo group and found no changes in stress levels, amount of sleep and cellphone usage as well as their correlations before and after taking placebo (Fig. 2D, 2E, 2F, 2G, 2H and 2I).

Correlations of wake-up mood/symptom vs stress levels and sleep duration: DHM improves wake-up mood/symptom

To investigate how sleep duration and stress levels affected next-day psychological wellbeing, we analyzed the survey data using the multiple regression model (1). The

"wake-up mood/symptoms" derived from the survey was used as the dependent variable Y_2 (taking negative values as negative feelings), and independent variables: before or after administration of DHM (X_1), stress levels (X_2), sleep duration (X_4).

$$Y_2 = -6.72 + 4.11X_1 - 0.84X_2 + 0.79X_4 + 0.20X_1X_2 - 0.50X_1X_4 + 0.086X_2X_4 - 0.063X_1X_2X_4 \quad (3)$$

As illustrated, we found a significant positive linear correlation of wake-up mood/symptom vs sleep duration and a negative correlation of wake-up mood/symptom vs stress level (Fig. 3A, 3B) with an interaction between sleep duration and stress levels. These results suggest that people experience better wake-up mood/symptoms when their sleep duration increases, which links to reduction in stress levels.

In addition to the reduced stress levels (Fig. 3A) and increased sleep duration (Fig. 3B), individuals taking DHM for 20 days reported a reduction in their negative feelings from -3.75 ± 0.17 to -1.38 ± 0.22 (Fig. 3E). There was an interaction between DHM administration and sleep duration on wake-up mood/symptoms (Fig. 3A). In contrast, minimal benefit was observed when individuals were administered placebo as illustrated by a lack of significant changes in wake-up mood/symptoms, stress levels, amount of sleep, or their correlations (Fig. 3C, 3D, 3E). Tables 3 and 4 show the effect size and statistical summary of our findings, respectively.

To understand if age plays a role in stress, time spent on cellphone, and sleep, we analyzed the correlations of stress levels, cell phone use, sleep duration, and wake up mood vs age before and after administration of DHM, as illustrated in Fig. 4. Data points were distributed evenly

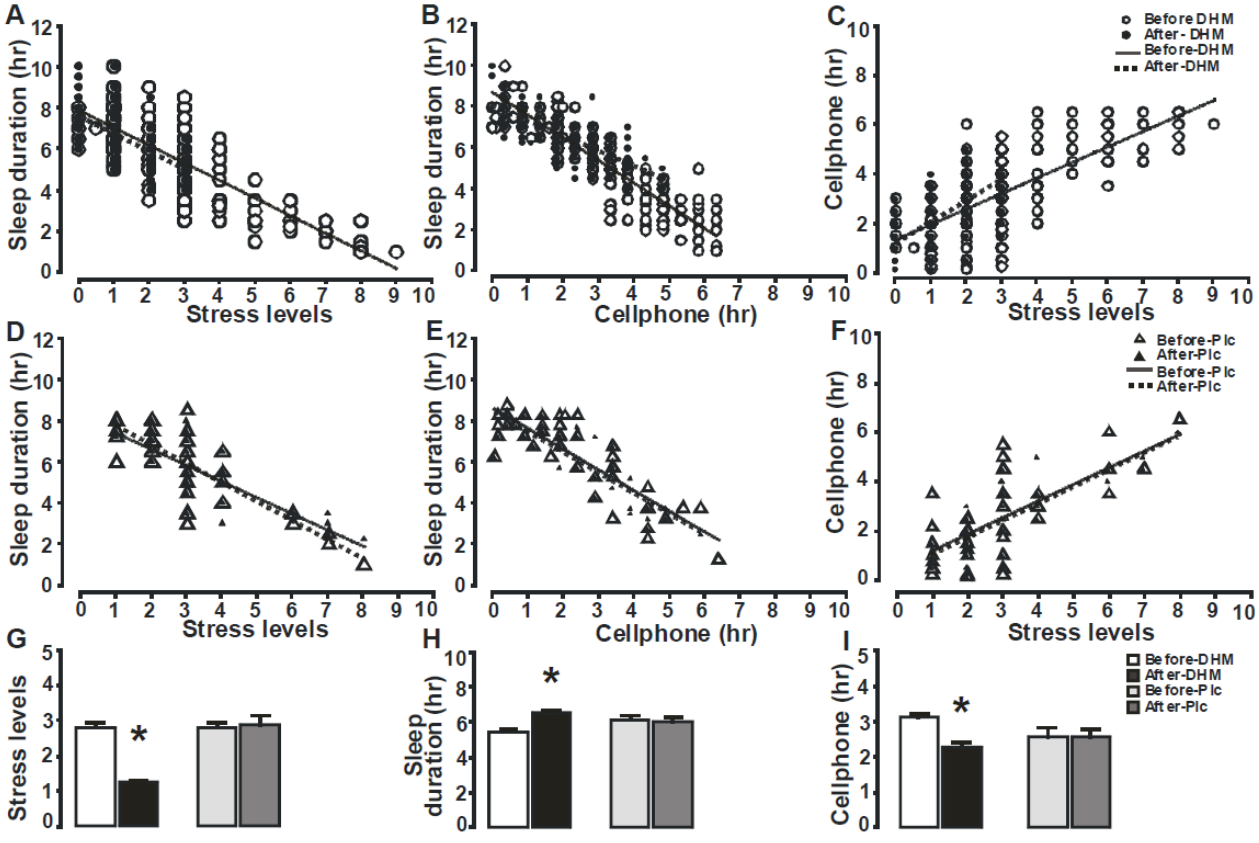

Figure 2 Negative linear correlations of sleep duration vs stress levels **(A)** and vs cellphone time **(B)** before and after DHM treatment for 20 days. **(C)** Positive correlation of cellphone use vs stress levels before and after DHM treatment. Correlations of sleep duration vs stress levels **(D)** and vs cellphone time **(E)** before and after placebo (Plc) administration for 20 days. **(F)** Positive correlation of cellphone uses vs stress levels before and after Plc**.** Lines and dotted lines denote regression lines. Summary of averaged stress level (**G**), sleep duration (**H**), and time spent on cellphone (**I**) before and after DHM/Plc (average mean ± SEM). *, $P \leq 0.05$.

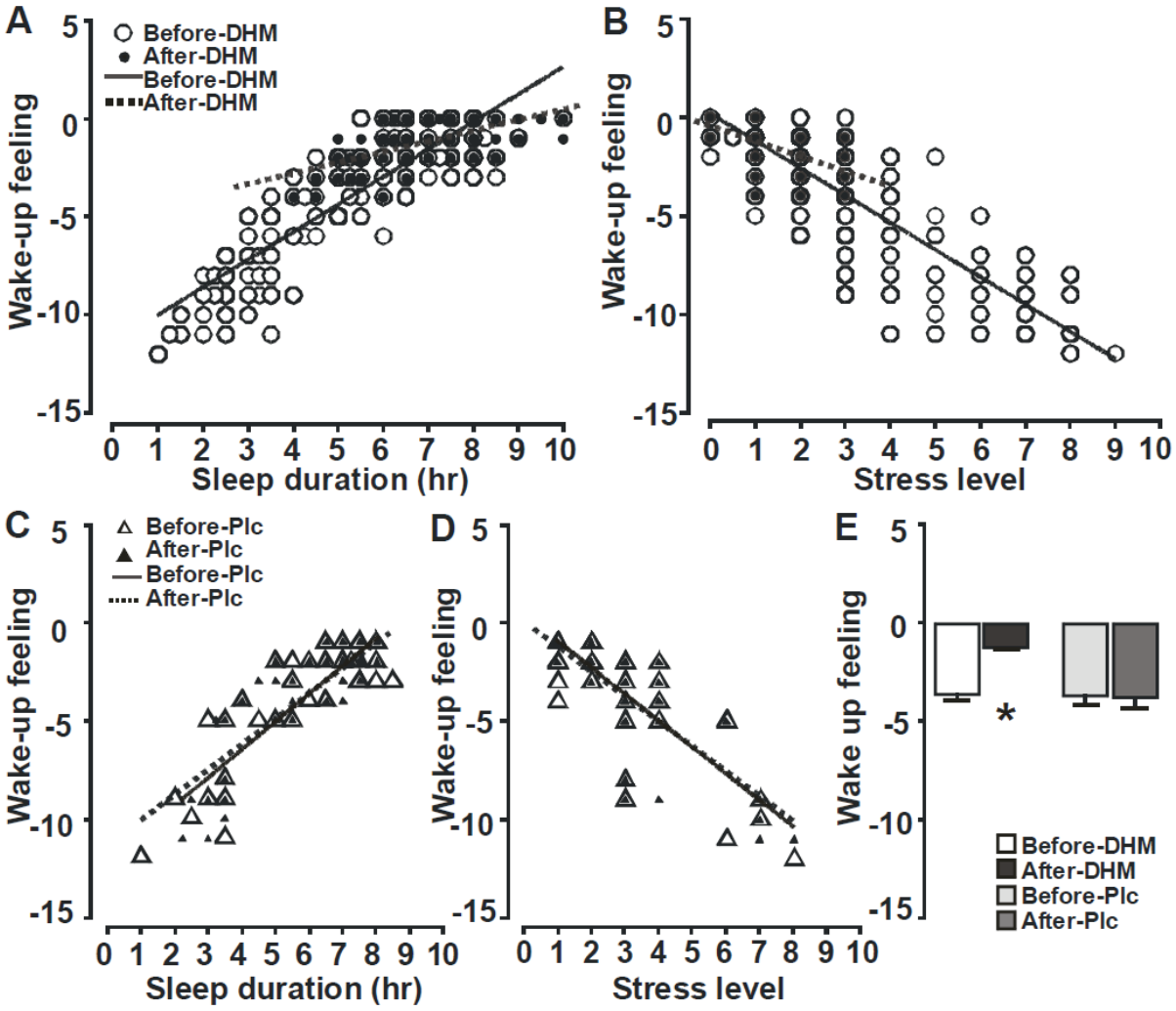

Figure 3. Feelings after waking up has a positive linear correlation with sleep duration (**A**) and a negative correlation with stress levels (**B**) before and after DHM treatment**.** The feelings after waking up has a linear correlation with sleep duration (**C**) and stress levels (**D**) before and after placebo. Lines and dotted lines denote regression lines. **E.** Summary of averaged negative feelings before and after DHM/placebo. (Average mean ± SEM). *, $P \leq 0.05$.

Table 3. Effect size

	Mean difference	Standard error (from ANOVA)	n	Standard deviation (pooled)	Effect size
Sleep duration	1.064	S1=0.113 S2=0.143	n1=244 n2=154	1.76878	0.60
Stress level	1.61	S1=0.103 S2=0.13	n1=244 n2=154	1.61	1.0
Cell Ph time	0.845	S1=0.0985 S2=0.124	n1=244 n2=154	1.53869	0.55
Wake up feeling	2.367	S1=0.171 S2=0.216	n1=244 n2=154	2.67473	0.885

Table 4. Summary and confidence intervals

		Mean	Standard error	95% Confidence Interval (CI)	
Sleep duration	Before DHM	5.454	0.113	5.23	5.675
	After DHM	6.518	0.143	6.237	6.80
Stress level	Before DHM	2.859	0.103	2.66	3.06
	After DHM	1.247	0.13	0.992	1.50
Cell Ph time	Before DHM	3.119	0.0985	2.926	3.31
	After DHM	2.274	0.124	2.03	2.517
Wake up feel	Before DHM	-3.750	0.171	-4.085	-3.415
	After DHM	-1.383	0.216	-1.806	-0.96

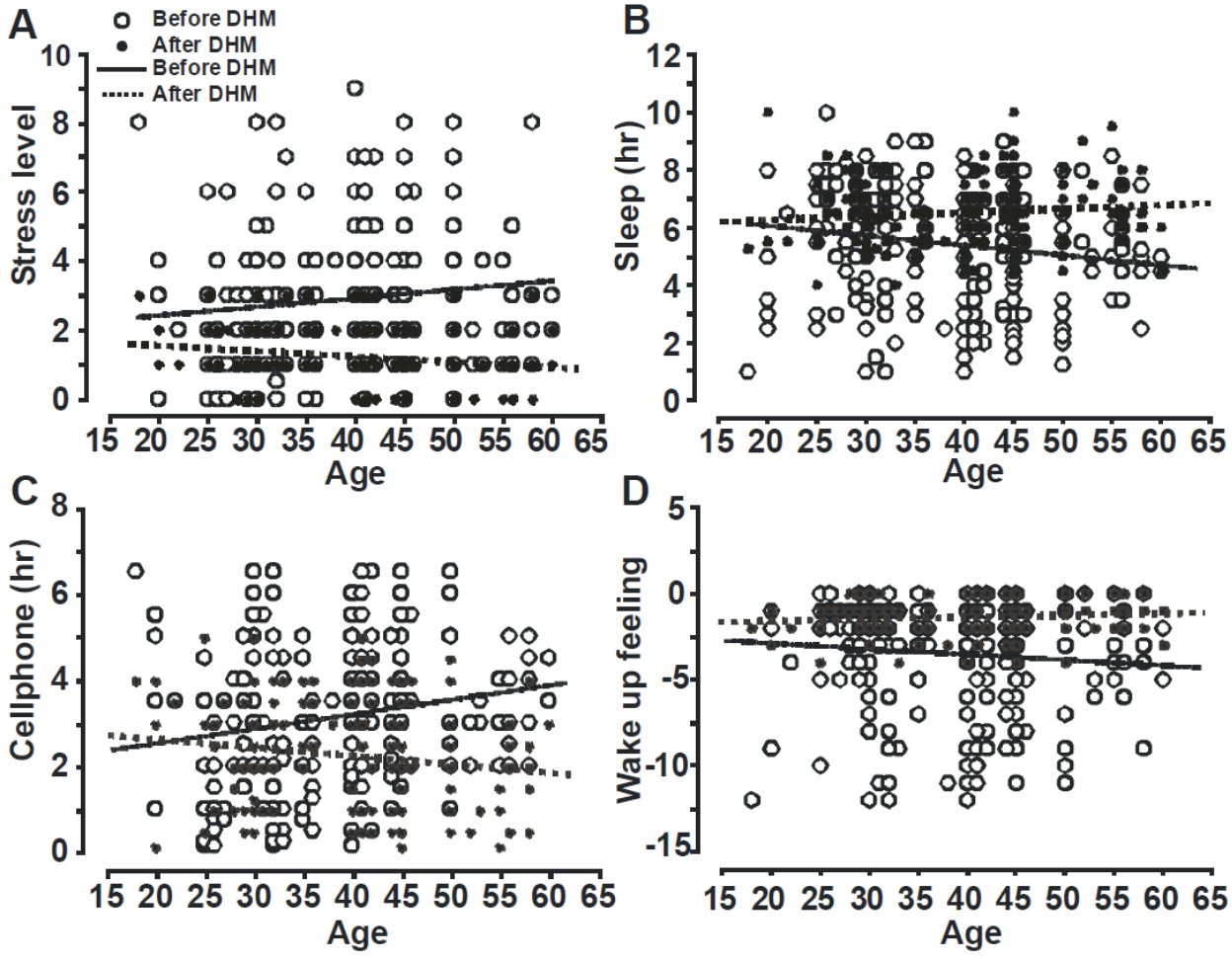

Figure 4. The relationship of stress levels vs age (**A**), sleep duration vs age (**B**), time spent on cellphone vs age (**C**), and wake-up feeling/ symptoms vs age (**D**) before and after DHM administration**.** Lines and dotted lines denote regression lines.

and showed no obvious trend across the age range. When we added age as an independent variable into our multiple regression models (Equations 2 and 3), there were no significant correlations between each of the four parameters vs age. All graphs showed small differences in the slopes of regression lines between before and after DHM administration and were not statistically significant. These results suggest that stress, time spent on cell phone, sleep, and wake up feelings are not age-dependent in the age range of our samples. Our samples included working adults in companies but did not include participants of very young or senior age.

DISCUSSION

In the present study, we tested the hypothesis that increased stress, anxiety, and time spent on cellphones negatively affect sleep and mood. In volunteers, we found negative linear correlations of sleep duration vs stress level and vs time spent on cellphones; a negative correlation of wake-up mood/symptom vs stress; and a positive correlation of sleep time vs wake-up mood/symptom. These findings provide a general understanding that duration or quality of sleep is correlated to the individual's level of stress or time spent on their cellphone. Daily intake of our herbal compound preparation "DHM" substantially improved 1) stress levels, 2) hours of sleep, 3) cellphone dependence, and 4) wake-up mood/symptoms. Stress levels, time spent on cell phone, sleep duration, wake-up mood/symptoms, and the effects of DHM were not age-dependent among individuals who are between 18 and 60 years old. As such, our findings can help guide ourselves and healthcare workers to better understand the problems involved in stress, sleep, and cellphone use, as well as to potentially alleviate these negative effects by herbal remedies like DHM.

As prescription medications require a visit to the doctor, they are not readily available to consumers and thus can hinder treatment processes of anxiety and stress. On top of the limited access, current anxiolytic medications on the market often do not result in remission (16). Developing novel drugs is not an efficient path to alleviation either, as marketing new drugs is costly and time consuming (44-46). In contrast, herbal remedies and dietary supplements can be made available to the public in a relatively short period of time because they do not require the extensive process of identifying targets, creating libraries of lead compounds, and validating targets (46). Thus, when shown to be effective, herbal remedies like DHM can advance human health relatively quickly and accessibly.

GABA is the main inhibitory transmitter in the central nervous system, and it is well known that $GABA_AR$ activation promotes sleep, anxiolysis, and stress reduction (47, 48). In our previous study, we demonstrated that insomnia has a linear correlation with $GABA_AR$ functions. In other words, when $GABA_AR$ is impaired, patients exhibit tolerance to the sedative/hypnotic actions of GABAergic drugs, including benzodiazepines, neurosteroids, and propofol (27). We have also demonstrated that $GABA_AR$ functions are impaired after anxiety and stress induced by social isolation (29). DHM, which we have shown to be a positive allosteric modulator of $GABA_ARs$, reduces anxiety levels in some animal models, including alcohol withdrawal, fetal alcohol syndrome, social isolation, and Alzheimer's disease (26, 28, 29).

This study may be subject to two limitations: 1) The data was based on an online self-reported survey; thus, measurements such as hours of sleep and cellphone usage were not entirely accurate. However, during the study, participants were randomly and blindly assigned to either DHM or placebo group. The researchers also had no direct interaction with the participants. Therefore, bias was minimized. Furthermore, given that most participants reported an improvement in their mental and emotional wellbeing after better hours of sleep, we can assume that the reports are fairly accurate. 2) We cannot conclude that these factors are the causes of each other—e.g., increased cellphone usage is correlated to decreased sleep duration, but does not necessarily indicate that cellphone use reduces sleep duration. Confounding factors such as positive life events may be related to these changes as well. Nonetheless, these associations shed some light on the impact of social isolation on mental wellbeing, and how DHM—directly or indirectly—can improve stress levels, sleep duration, and overall wellbeing.

CONCLUSIONS

Although the scale of this survey is relatively small, combined with our previous findings, we have demonstrated the health and psychological challenges associated with social isolation including sleep disorders and stress. Our study illustrates the benefits of a dietary supplement for alleviating stress, anxiety, and sleep deficits, especially during the stressful times of the COVID-19 pandemic. Large-scale investigations in the future will provide a clearer understanding of these relationships as well as the beneficial mechanisms of DHM and related herbal remedies.

ABBREVIATIONS

BZ	benzodiazepine
CNS	central nervous system
COVID-19	Coronavirus disease 2019
DHM	dihydromyricetin
GABA	gamma-aminobutyric acid
$GABA_AR$	gamma-aminobutyric acid A receptor
MMRMA	mixed model repeated measures analysis of variance
PAM	positive allosteric modulator

DECLARATIONS

Ethics approval and consent to participate

The studies were reviewed and approved by the University of Southern California Institutional Review Board (IRB Record ID: UP-21-00653). The participants provided their written informed consent to participate in this study. This study adheres to CONSORT guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

A.S.S. discussed the survey design, analyzed data, worked on the protocol, and wrote manuscript. S.W. discussed the survey design, worked on IRB application and protocol, and wrote manuscript. A.A.O. discussed the survey design, collected data, and wrote manuscript. A.S.S. and S.W. equally contributed as the first author. E.H. programmed the online survey. M.A. discussed the design of the survey form. Z.Z. and C.X. collected and analyzed data and wrote manuscript. J.W., K.Z. (Kaiying Zhang), and L.L. collected and analyzed data. K.Z. (Ke Zhang) organized survey and collected data. T.D.C. provided regulatory and quality control support, wrote document of IRB application. C.P. hypothesized, designed, organized survey, and collected and analyzed data. X.M.S. discussed the survey design, performed statistical analyses, and wrote manuscript. J.L. hypothesized, designed, and organized survey; collected and analyzed data, statistical analyses; and wrote manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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