ORIGINAL ARTICLE

Impacts of Social Distancing and a Potential Remedy: A Randomized Double-blind Placebo-controlled Study

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ABSTRACT

Objectives: To gain insight into how social distancing impacts human life and how it may induce stress, anxiety, depressive-symptoms, sleep disturbance, and mental challenges during the pandemic; and to evaluate the effects of a complementary therapy named Smarto-One on improving these health impacts.

Methods: Participants, men and women aged 20-65, were randomly assigned to the interventional Smarto-One group (n=259) or placebo group (n=68). Participants orally self-administered Smarto-One or placebo for 20 consecutive days. Online surveys were completed by the participants the day before the 20-day treatment start date and the day following treatment end date. Fifteen participates from Smarto-One group and fifteen participates from placebo group participated in electroencephalography (EEG) during sleep before and after the 20-day intervention. The primary outcome measures were sleep duration and self-evaluated stress.

Results: We found 1) during social distancing due to the COVID-19 pandemic, stress/depression led to sleep disturbance and mental issues; 2) participants taking Smarto-One showed significant improvements in stress/depression levels, sleep duration and wake-up mood/symptoms compared to placebo; and 3) participants taking Smarto-One showed significantly improved deep sleep time (slow-wave sleep, SWS, N3) of non-rapid eye movement (non-REM) sleep as measured by EEG.

Conclusions: This study illustrates the value of Smarto-One as an effective remedy that improves mental health and well-being under conditions including social distancing and stress/depression. (*Int J Biomed Sci* 2023; 19 (2): 37-45)

Keywords: Social Distancing induced negative outcome; stress; anxiety; depression; sleep problem; potential remedy

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INTRODUCTION

Social relationships considered emotionally supportive may act as a buffer against the effects of stress (1, 2). Social interactions are pivotal for both our mental and physical health, affecting biological functioning and positively influencing health behaviors (3-5). Research on human social behavior has advanced our understanding of how the brain regulates emotion and cognition. Since humans are often described as "social creatures", social connection is crucial to development, health, and wellbeing. Notably, the impact of the loss of social connection, related to social distancing, on human health has not been adequately studied. This issue is of critical importance in that social distancing has been linked to serious health conditions (6, 7)—one that is increasingly believed to have both emotional and physical consequences. Accumulating evidence links social distancing to negative outcomes on health, including induction of anxiety along with depression and poor cognitive performance (8, 9); memory loss (10, 11); increased suicidal behaviors (12, 13); increased mortality in older adults (14-16); and disruptions of the cardiovascular and immune systems (5).

Over the past several years, the rapid spread of the novel coronavirus disease (COVID-19) has led to business disruptions, unanticipated deaths, and disruption of the lives of billions of people around the world, resulting in a severe economic downturn (17-19). These result in unhealthy changes in stress and anxiety/depression related to health physical wellbeing, employment disruption, and economic hardship, all of which were exacerbated by social distancing regulations (20-23).

We spend approximately one-third of our lives sleeping, and interruptions to adequate and restful sleep can have detrimental effects on health and mental health (24). The relationship between stress, sleep, and mental wellbeing and how they affect daily life are not well understood. As such, this gap in our knowledge needs further investigation.

Depressive symptoms are persistent negative mood, loss of interest in things normally enjoyed, feelings of sadness, hopelessness, or emptiness, naturally feel down from time to time. It is the negative emotional state characterized by worry and apprehension, associated with specific physical, cognitive, and behavioral manifestations (25, 26). Research has found that people who experience major depression often have lower levels of the neurotransmitter

γ-Aminobutyric acid (GABA) which is the major inhibitory neurotransmitter in the central nervous system (CNS). It is well appreciated that GABAergic transmission plays an important role in anxiety responses and sleep regulation in normal and pathological states (27). There are four sleep stages, including three (N1, N2 and N3) that form non-rapid eye movement (NREM) sleep and one for REM sleep. N3 is also referred to as deep sleep and slow-wave sleep (SWS). The body cycles through all of these stages approximately 4 to 6 times each night sleep, averaging 90 minutes for each cycle (28). Sleep leads to mental relaxation due to the action of GABA (29). A person falls asleep and then cycles from light sleep to deep sleep. This stage is when a person's brain activity, breathing, and heart rate slow down, body temperature drops, muscles relax, and eye movements minimize. Sleep supports almost every system of the body (30-32) and maintains good health. Enhancement of GABAergic neurotransmission and $GABA_A$ receptors ($GABA_ARs$) plays an important role in sleep initiation and maintenance (29, 33). Therefore, a common treatment for sleep problems is the enhancement of $GABA_ARs$ by allosteric modulators of $GABA_ARs$ such as benzodiazepines (BZ) (34). However, long-term use of BZs can result in unwanted adverse events including addiction risk, tolerance, morning sleepiness, and increased suicidal consciousness (35).

Our group has systematically studied the benefits of plants and herbs as alternatives to prescription drugs (36). We've also developed a formula called Smarto-One that contains flavonoids derived from herbs. We have shown that Smarto-One potentiates $GABA_ARs$ that can counteract anxiety/aggression and depressive symptoms with at least a portion of these outcomes via activity on $GABA_AR$ (30). Notably, we found various flavonoid extracts that relieve stress and anxiety (36, 37).

Social distancing during the COVID-19 pandemic has affected everyone, causing anxiety, stress, nervousness, and difficulty sleeping, while many were denied access to medical care due to social distancing orders (20, 38-41). Thus, we asked if there were any alternative complementary treatments to address these issues. First, we conducted an online survey. With this survey, we aimed to understand levels of stress and anxiety, and to investigate related stressors during social distancing. We then introduced Smarto-One, an herbal combination, to participants who were willing to voluntarily evaluate its stress-relieving and sleep-improving effects. To determine the effect on sleep

improvement, 15 participants in the Smarto-One group and 15 in the placebo group took electroencephalograms (EEGs) during sleep before and after the 20-day intervention. The goal of our work was to explore the potential of using Smarto-One to help improving sleep, including relaxation → sleepiness → and deep sleep, as assessed by self-report surveys and confirmed by EEG.

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.

In this study, we utilized an online survey that was used in the previous study (42), which has been evaluated by clinical trials. This survey was designed to assess the changes, focusing on stress/anxiety/depressive symptoms, in sleep, and emotional states in a larger group of participants. Participants who were willing to evaluate the effects of Smarto-One on alleviating stress and improving sleep quality were enrolled in the study. Participants were randomly placed into two cohorts either the Smarto-One or the placebo (blind to the participants).

Stress is a response to external factors that may exceed an individual's resources, affecting an individual's emotional state or ability to perform day-to-day tasks (43-45). Stress and depression can share some similarities, they have distinct characteristics. Depression is a mental health condition that involves a persistent and pervasive sense of sadness, hopelessness, or feelings of worthlessness, apathy. Therefore, we summarized common stressors and categorized stress, sleep characters into eight categories (Table 1).

To quantify the stress level, the cumulative score of the 13 responses to item #3 in the survey form was used where "yes" was scored as 1 point, "no" was scored 0.

To quantify the depressive feelings after waking up, the cumulative score of the 24 responses to item 8 in the survey where "yes" was scored as -1 point, "no" was scored as 0 points, and "not sure" was scored as -0.5 points, except the first question "refreshed" where "yes" was scored as 1, "no" was scored as 0, and "not sure" was scored as 0.5. The more negative the accumulative score is, the greater the depressive symptoms. All causes of stress were considered as independent factors affecting sleep duration (46). Sleep time was calculated as follows: Actual sleep time = Bedtime - Time spent trying to fall asleep.

The volunteer participants

The survey was collected from male (40%) and female (60%) participants (total 327) aged 20 to 65 in Beijing and Suzhou, China. Participants are randomly assigned a number, 1 or 2 (1 for Smarto-One treatment and 2 for placebo) (Table 2). Participants were blinded to the treatment corresponding to each number. Participants' education level was above high school. Final data were selected from those who received the informed consent, were able to complete the survey, were between the ages of 20 and 65 at the time of consent, as well as had no alcohol, drug use, COVID-19 infection, or other underlying chronic medical conditions, or were currently use prescription medicines, including antidepressants. Exclusion criteria also included pregnant or breastfeeding women, use of a current sleep prescription, reports of at least 3 naps per week, and a history of sleep apnea. Medical history was self-reported. Recruitment began on July 1, 2021, and ended on December 31, 2021, on a rolling recruitment led by one of our team members. Participants were instructed to take either a placebo or Smarto-One at the same time each day. Treatment was given once daily for 20 days without crossover, with a follow-up survey the day after the end of the 20-day intervention.

To determine the effects on sleep pattern, 15 participants in the Smarto-One group and 15 in the placebo group whose Pittsburgh Sleep Quality Index (PSQI) (47)>5 took electroencephalograms (EEGs) during sleep before and after the 20-day intervention. 11 participants in the placebo group and 12 in the Smarto-One group completed the EEG test.

Treatment preparation

The placebo contained excipients including extracts of celery, strawberry, oranges, rose, and beet blended in powder form of 1 g. The Smarto-One formula contained proprietary blend of 400 mg, Thiamine 3 mg, Pyridoxine 3.5 mg, Citric Acid, Lemon extract, *Hovenia Dulcis* extract, plus same excipients as placebo.

Statistical Analyses

The data are presented as mean ± SD in the text of Results section. The effects of Smarto-One/placebo was analyzed with two-way repeated measures ANOVA with repeated measures on one factor (before and after treatment) followed by multiple comparison (Holm-Sidak method). $p \leq 0.05$ was considered statistically significant.

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 [ ] Work/career [ ] School/study [ ] Relationships (e.g., friends, family, partner, co-workers) [ ] Financial problems [ ] Environment (e.g., noise, air quality, light, natural or manmade 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 (palpitation) [ ] 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

Table 2. Baseline demographics and clinical characteristics for each group

	Smarto-One	Placebo	Total
Age range	20-65	20-65	
Median	40	38	
N	259	68	327
Gender	%	%	
Male	63	37	
Female	51	49	

RESULTS

Smarto-One improves stress levels during social distancing

To gain insight into how social distancing impacts human life and how it may induce stress, depression, sleep, and mental challenges during the pandemic, we organized this survey study. During social distancing, the average stress level before intervention was 3.85 ± 1.7 in placebo group, and 3.87 ± 1.54 in Smarto-One group. After daily administration of placebo or Smarto-One once per day for 20 days, the average stress level was 3.85 ± 1.37 in placebo group, and 1.85 ± 1.02 in Smarto-One group (Fig.
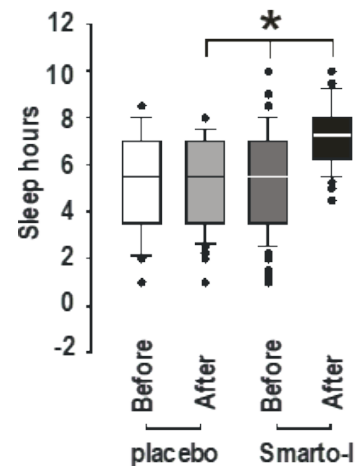
1). These results suggest that Smarto-One administration ameliorates social distancing-induced stress.

Smarto-One improves sleep during social distancing

During the COVID-19 pandemic, most people experienced increased stress/depression levels, partially due to social distancing. As an outcome of the social distancing, unhealthy consequences such as reduction in quality sleep time and negative mood were prominent (12, 13). As presented in Fig. 2, we found that the average sleep duration before the intervention was 5.36 ± 2.04 hours in placebo group, and 5.32 ± 1.98 hours in Smarto-One group. After daily administration of placebo or Smarto-One once per day for 20 days, the average sleep duration become 5.31 ± 1.86 hours in placebo group, and 7.25 ± 1.37 in Smarto-One group (Fig. 2).

Smarto-One improves depressive symptoms during social distancing

We also evaluated depressive symptoms during social distancing. We found that (Fig. 3) the average depressive symptoms after waking up in baseline conditions (before treatment) was -4.54 ± 2.43 in placebo group, and -4.62 ± 2.63 in Smarto-One group. After daily administration of placebo or Smarto-One once per day for 20 days, the average depressive symptoms become -4.43 ± 2.28 in pla-

Figure 1. Effects of social distancing and administration with Smarto-One (Smarto-I) on stress levels evaluated by scores of 'Item #3' in the survey form. Two-way repeated measures ANOVA followed by multiple comparison, Holm-Sidak method. Between Treatments, $*$, $p \leq 0.05$. The left two boxplots are before and after placebo (n=68). The right two boxplots are before and after Smarto-One (n=259).

Figure 2. The effects of social distancing and administration with Smarto-One (Smarto-I) on sleep duration evaluated by self-report in Item #6 of the survey form. Two-way repeated measures ANOVA followed by multiple comparison, Holm-Sidak method. Between Treatments, $*$, $p \leq 0.05$. The left two boxplots are before and after placebo (n=68). The right two boxplots are before and after Smarto-One (n=259).

cebo group and -1.45 ± 1.04 in Smarto-One group (Fig. 3). These results suggest that sleep and mental issues during social distancing can be ameliorated by Smarto-One administration.

**Smarto-One improved deep sleep—SWS as measured by EEG**

EEG was recoded to evaluate sleep quality (48-50) and to determine the effects of Smarto-One on the sleep patterns in patients classified as "poor sleepers" (PSQI >5). We performed EEG analysis before and after placebo or Smarto-One treatment period. We found that on average, SWS length before treatment was 12.7 ± 8.23 minutes (min) per sleep cycle in placebo group, and 6.06 ± 5.55 min/cycle in Smarto-One group. After daily oral administration of placebo or Smarto-One once per day for 20 days, the average SWS length become 6.65 ± 5.84 min/cycle in placebo group, and 17.8 ± 11.87 min/cycle in Smarto-One group (Fig. 4). These results suggest that increased stress/depression during social distancing impact the quality of sleep, while Smarto-One administration improves deep sleep.

DISCUSSION

In the present study, we investigated the potential of Smarto-One as a compound remedy to reduce some of the consequences of social distancing from the COVID 19 pandemic. In agreement with previous work, we found that unwanted stress, anxiety, and depressive symptoms during social distancing in the pandemic may translate into changes in sleep and mood disturbances. These findings provide a general understanding that duration or quality of sleep is related to the individual's level of stress/depression. Our major findings are that the natural formula remedy "Smarto-One", as a complementary therapy, improve 1) stress/depression levels; 2) depressive symptoms; as well as 3) sleep duration and sleep quality as elevated deep sleep in "poor sleepers".

As prescription medications require a visit to the medical facility, they are not readily available to individuals with health issues and thus can hinder treatment processes of anxiety and stress. In addition to the limited access, current anxiolytic medications on the market often do not result in remission and can lead to adverse side effects including addiction risk, tolerance, morning sleepiness, and increased suicidal consciousness (35, 51). On the other hand, developing novel drugs to address the above health issues is not an efficient path to alleviation, as discovery, development and marketing of a new drug is costly and time consuming (52-54). 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 (54). Thus, when shown to be effective, herbal remedies like
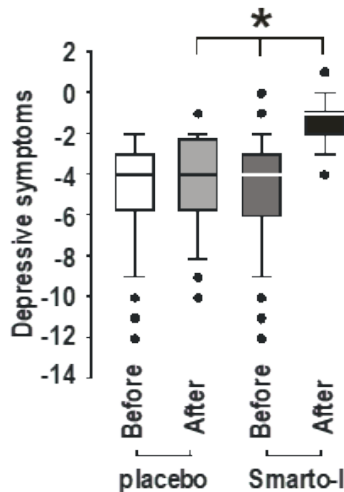
Figure 3. The effects of Smarto-one (Smarto-I) on depressive symptoms after waking up evaluated by accumulated scores in Item #8 of the survey. Two-way repeated measures ANOVA followed by multiple comparison, Holm-Sidak method. Between Treatments, *, $p < 0.05$. A) The changes of sleep hours before and after placebo (n=68) or Smarto-One (Smarto-I, n=259).
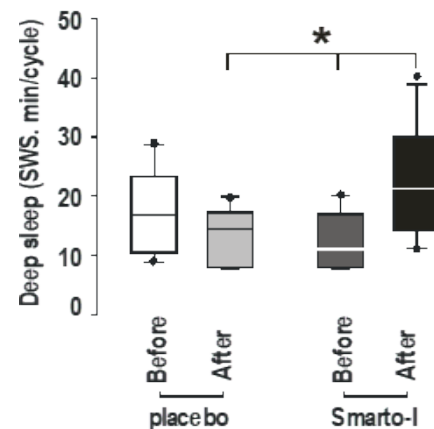
Figure 4. The effects of Smarto-One (Smarto-I) on deep sleep (Slow Wave Sleep, SWS) as measured by EEG. Two-way repeated measures ANOVA followed by multiple comparison, Holm-Sidak method. Between Treatments, *, $p \leq 0.05$. n = 11 for placebo group and n = 12 for Smarto-One group.

Smarto-One can advance human health relatively quickly and accessibly.

GABA is the main inhibitory transmitter in the brain, and it is well known that $GABA_AR$ activation promotes sleep, anxiolysis, and stress reduction (55, 56). In our previous study, we demonstrated that insomnia correlates 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 (57). We have also demonstrated that $GABA_AR$ functions are impaired after anxiety and stress induced by social distancing (37). Smarto-One, which contains a component that 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 (37, 58, 59).

Although our investigation showed great promise for the use of Smarto-One, there are some limitations that should be mentioned. First, data presented and used for analysis were based on online self-report surveys and limited number of EEG tests. Therefore, measurements such as sleep time may not fully represent the scope or degree of issues raised by social distancing. The limited number of participants receiving the EEG evaluation might not be able to fully capture the characteristics of sleep disturbance in general population. In an attempt to reduce the impact of this limitation, for the study design, participants were randomly selected and assigned to experimental groups in a blinded fashion. The EEG findings provide an initial outcome regarding the effects of social distancing and anxiety on sleep as well as the potential of Smarto-One as a therapeutic for sleep disturbance. Secondly, clinicians and researchers did not directly interact with the participants. Therefore, deviations are minimized. Also, given that most participants reported improvements in their mental and emotional well-being after getting more sleep, we can assume these reports are fairly accurate. Third, confounding factors such as life events may also be associated with these changes. Still, the associations shed light on the impact of social distancing on mental health, and how Smarto-One — directly and indirectly — improved stress/depression levels, sleep duration, and overall health.

Combined with our previous findings, we can see an emerging pattern of changes in health and psychological challenges associated with social distancing, including sleep disturbances and stress/depression. Collectively, our research illustrates the potential benefits of complementary therapies in relieving stress, anxiety, depressive symptoms, and sleep loss, especially during stressful times of the COVID-19 pandemic. Future large-scale investigations will provide a clearer understanding of these effects due to social distancing, as well as the beneficial mechanisms of Smarto-One and related herbs.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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