Complementary Therapies in Medicine 41 (2018) 47–51

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Effect of crocetin on quality of sleep: A randomized, double-blind, placebo-controlled, crossover study

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ARTICLE INFO

Keywords:
Crocetin
Gardenia yellow
Sleep quality
Electroencephalogram

ABSTRACT

Objectives: The aim of the present study was to investigate the effect of crocetin on sleep architecture and subjective sleep parameters in healthy adult participants with mild sleep complaints.
Design: A randomized, double-blind, placebo-controlled, crossover study with two intervention periods of 14 days each, separated by a 14-day wash-out period.
Interventions: Thirty participants were randomly assigned to one of two sequence groups. Each group was given crocetin at 7.5 mg/day, or placebo. We measured objective sleep parameters using single-channel electroencephalography and assessed subjective sleep parameters using the Oguri–Shirakawa–Azumi Sleep Inventory, Middle-age and Aged version (OSA-MA).
Main outcome measures: Differences between crocetin and placebo in an objective sleep parameter (delta power), and OSA-MA scores.
Results: Delta power was significantly increased with crocetin compared with placebo. There were no significant differences in the other sleep parameters, including sleep latency, sleep efficiency, total sleep time, and wake after sleep onset. Subjective scores for sleepiness on rising and feeling refreshed were significantly improved with crocetin compared with placebo.
Conclusions: The findings of the present study suggest that crocetin supplementation contributes to sleep maintenance, leading to improved subjective sleep quality.

1. Introduction

Although the functions of sleep are not all fully understood, it is commonly accepted that sleep is essential for physical and mental health and that it plays an important role in recovery from illness and injury. There is growing evidence of close associations between inadequate or poor-quality sleep and diseases such as hypertension,[1] diabetes,[2] and depression.[3] In addition, sleepiness due to inadequate sleep may result in poorer performance of tasks or even in serious accidents, such as driving-related accidents.[4]

Deep sleep, also referred to as slow-wave sleep or delta sleep, is characterized by low frequency waves (delta waves) on electroencephalogram (EEG) recordings. This stage of sleep is thought to have a different function from those of other sleep stages and to be more intensive.[5] It has been reported that decreased deep sleep EEG activity (delta activity), quantified as the EEG spectral power in the delta frequency range (delta power), is associated with sleep complaints.[6] Experimental disruption of deep sleep has been shown to cause increasing daytime sleepiness and diminished performance.[7] Conversely, pharmacologically enhanced delta activity contributes to improve sleep maintenance and subjective sleep quality.[8] It has therefore been hypothesized that deep sleep and delta activity are a determinant of sleep quality.[8,9]

Crocetin, a type of carotenoid, is an aglycone of crocin found in the fruit of gardenia (*Gardenia jasminoides* Ellis or *Gardenia augusta* Merrill) and the stigma of saffron (*Crocus sativus* L.). In Asian countries such as Japan and China, people have been using carotenoid pigments extracted from gardenia fruit, often referred to as “gardenia yellow,” as a natural colorant in foods for centuries. Gardenia fruit has been used as a traditional herbal medicine, and crocetin and crocin have been reported to possess various pharmacological properties, including anti-oxidation[10] and anti-inflammatory[11] activity, the attenuation of physical

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https://doi.org/10.1016/j.ctim.2018.09.003
Received 24 July 2018; Received in revised form 3 September 2018; Accepted 4 September 2018
Available online 08 September 2018
0965-2299/

fatigue,[12] and reduction of the symptoms of depression.[13] Pharmacokinetic studies have shown that orally administrated crocin is hydrolyzed to crocetin before or during intestinal absorption, and it is found as crocetin in blood.[14] Crocetin can cross the blood–brain barrier and enter the central nervous system (CNS),[10,15] and it is thought that crocetin can affect CNS activity.

A previous sleep study found that taking crocetin reduced the number of wakening episodes during the sleep period.[16] That study used actigraphy, a method for monitoring locomotor activity that can estimate the state of wakefulness or sleep, but which cannot access sleep architecture or sleep staging.[17] The present study used EEG recording and a sleep questionnaire to investigate the effect of crocetin on sleep architecture and subjective sleep parameters in healthy adult participants with mild sleep complaints.

2. Methods

2.1. Study design

This study followed a randomized, double-blind, placebo-controlled, crossover design. The study comprised a 5-day initial period (the baseline assessment period) followed by two crossover 14-day intake periods separated by a 14-day wash-out period (Fig. 1). The dosage of crocetin at 7.5 mg per day was determined based on a previous study.[16] Although the elimination of crocetin from the CNS is unclear, the half-life of crocetin in the blood has been reported to be 6–7 h.[18] Thus, it was assumed that crocetin would be completely washed out by the end of the 14-day wash-out period. This study was conducted from January to March 2017.

The study was approved by the Oriental Ueno Detection Center Ethics Committee (approval No. 2016-42) and the study protocol was registered with University Hospital Medical Information Network Clinical Trials Registry (UMIN000025854). This study was conducted in accordance with the principles of the Declaration of Helsinki and the national guidelines of Japan (Ethical Guidelines for Medical and Health Research Involving Human Subjects). Written informed consent was obtained from all the participants before any study procedures were initiated.

2.2. Test supplements

Gardenia yellow, containing a high concentration (≥75%) of crocetin, was obtained from Riken Vitamin Co., Ltd (Tokyo, Japan). Test supplements were formulated as soft capsules filled with edible oil, emulsifier, and gardenia yellow. Each capsule contained 7.5 mg of crocetin. The placebo capsules were identical to the test capsules apart from replacing the gardenia yellow with dextrin. The test and placebo capsules were indistinguishable in appearance, flavor and packaging.

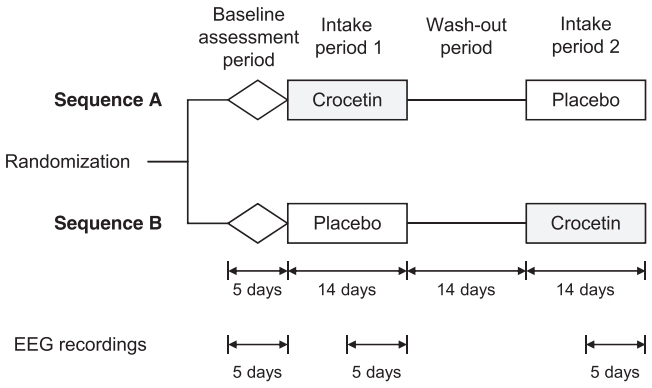

Fig. 1. Schematic overview of the study design.

2.3. Participants

The participants were recruited from the volunteer database of TES Holdings Co., Ltd. (Tokyo, Japan). The inclusion criteria were as follows: healthy men and postmenopausal women aged 35–60 years; mild sleep complaints; and a regular lifestyle, with regular lights-out and wake-up times, sleeping for > 4 h per night, working during the daytime from Monday to Friday, and having Saturday and Sunday off work. The exclusion criteria were as follows: body mass index > 25 kg/m^2 (to exclude suspected obstructive sleep apnea and metabolic syndromes); excessive intake of alcohol; a smoking habit; serious anemia; possible allergy to the raw materials of the test supplements, such as soybean-originated emulsifier, and hypersensitivity to the electrode pad of the EEG device; the use of medication or medical apparatus for any clinical treatment of disease; known or suspected sleep apnea syndrome, nocturia, benign prostatic hyperplasia, or an overactive bladder; a history of a major disease such as liver, heart, kidney or digestive system disease; and anyone judged unsuitable by the physician in charge. Those who met these criteria were enrolled in the study.

The participants were required to visit the clinic (Oriental Ueno Detection Center, Tokyo, Japan) for screening, where they were assessed for eligibility and their health condition was assessed with a physical examination, blood test, blood biochemical test, urine analysis, and medical interview. They were also administered a sleep questionnaire, the Oguri–Shirakawa–Azumi Sleep Inventory, Middle-age and Aged version (OSA-MA), described later. The participants were fully informed of the contents of capsules and about the study methods prior to providing written informed consent.

2.4. Randomization

The participants were randomly allocated (1:1) to one of two sequences using a computer-generated randomization list prepared by dedicated staff at a contract research organization, who had no further role in the study. Randomization was stratified by age, sex, and OSA-MA factor 2 score (initiation and maintenance of sleep) at screening. The randomization list and related documents were kept in a secure location within the contract research organization. The investigator, clinical staff, participants, and anyone else directly involved in the conduct of the study, including those assessing the outcomes, were blinded to the sequence allocation code, which was not opened until the database was locked.

2.5. Procedure

The participants visited the clinic on three occasions: at the start of the 5-day baseline assessment period and after each intake period. At each visit, the participants underwent a physical examination and clinical interviews. During the intake periods, each participant took one capsule daily with water after the evening meal. Sleep EEG data were recorded at the participant's home for five consecutive nights (from Monday to Friday) during the baseline assessment period and during the final five days of each intake period (Fig. 1). The participants were not permitted to drink alcohol during the days on which the EEG recordings were performed and were asked to complete the OSA-MA upon waking each morning after EEG recording.

During the study period, the participants were instructed to take the test supplements daily and were asked, as far as possible, not to change their lifestyle habits, such as sleeping patterns, diet, and exercise. The participants were also asked to record their activities and health condition in a daily diary.

2.6. Measurements and analysis of EEG data

The primary efficacy endpoint of this study was defined to be the change in delta power. The secondary efficacy endpoints were other