別紙様式（Ｖ）－１

機能性の科学的根拠に関する点検表

１．製品概要

商品名	快眠サポート
機能性関与成分名	L-セリン
表示しようとする機能性	本品にはL-セリンが含まれるので、睡眠の質の向上（寝つきの改善、熟眠感の改善、起床時の満足感）に役立ちます。日常生活のストレスによる一時的な睡眠の不満を持つ方におすすめです。

２．科学的根拠

【臨床試験及び研究レビュー共通事項】

☑（主観的な指標によってのみ評価可能な機能性を表示しようとする場合）当該指標は日本人において妥当性が得られ、かつ、当該分野において学術的に広くコンセンサスが得られたものである。

□（最終製品を用いた臨床試験又は研究レビューにおいて、実際に販売しようとする製品の試作品を用いて評価を行った場合）両者の間に同一性が失われていないことについて、届出資料において考察されている。

☑最終製品を用いた臨床試験

（研究計画の事前登録）

□UMIN 臨床試験登録システムに事前登録している[注1]。

□（海外で実施する臨床試験の場合であってUMIN 臨床試験登録システムに事前登録していないとき）WHO の臨床試験登録国際プラットフォームにリンクされているデータベースへの登録をしている。

（臨床試験の実施方法）

□「特定保健用食品の表示許可等について」（平成 26 年 10 月 30 日消食表第 259 号）の別添２「特定保健用食品申請に係る申請書作成上の留意事項」に示された試験方法に準拠している。

☑科学的合理性が担保された別の試験方法を用いている。

→☑別紙様式（Ｖ）－２を添付

（臨床試験の結果）

□国際的にコンセンサスの得られた指針に準拠した形式で査読付き論文として公表されている論文を添付している[注1]。

□（英語以外の外国語で書かれた論文の場合）論文全体を誤りのない日本語に適切に翻訳した資料を添付している。

☑研究計画について事前に倫理審査委員会の承認を受けたこと、並びに当該倫理審査委員会の名称について論文中に記載されている。

□（論文中に倫理審査委員会について記載されていない場合）別紙様式（Ｖ）

－３で補足説明している。

☑掲載雑誌は、著者等との間に利益相反による問題が否定できる。

□最終製品に関する研究レビュー
□機能性関与成分に関する研究レビュー

□（サプリメント形状の加工食品の場合）摂取量を踏まえた臨床試験で肯定的な結果が得られている。
□（その他加工食品及び生鮮食品の場合）摂取量を踏まえた臨床試験又は観察研究で肯定的な結果が得られている。
□海外の文献データベースを用いた英語論文の検索のみではなく、国内の文献データベースを用いた日本語論文の検索も行っている。
□（機能性関与成分に関する研究レビューの場合）当該研究レビューに係る成分と最終成分の同等性について考察されている。
□（特定保健用食品の試験方法として記載された範囲内で軽症者等が含まれたデータを使用している場合）疾病に罹患していない者のデータのみを対象とした研究レビューも併せて実施し、その結果を、研究レビュー報告書及び別紙様式（Ⅰ）に報告している。

□表示しようとする機能性の科学的根拠として、査読付き論文として公表されている。

□当該論文を添付している。
□（英語以外の外国語で書かれた論文の場合）論文全体を誤りのない日本語に適切に翻訳した資料を添付している。

□PRISMA 声明（2009 年）に準拠した形式で記載されている。
□（PRISMA 声明（2009 年）に照らして十分に記載できていない事項がある場合）別紙様式（Ⅴ）－３で補足説明している。
□（検索に用いた全ての検索式が文献データベースごとに整理された形で当該論文に記載されていない場合）別紙様式（Ⅴ）－５その他の適切な様式を用いて、全ての検索式を記載している。
□（研究登録データベースを用いて検索した未報告の研究情報についてその記載が当該論文にない場合、任意の取組として）別紙様式（Ⅴ）－９その他の適切な様式を用いて記載している。
□食品表示基準の施行前に査読付き論文として公表されている研究レビュー論文を用いているため、上記の補足説明を省略している。

□各論文の質評価が記載されている[注２]。
□エビデンス総体の質評価が記載されている[注２]。
□研究レビューの結果と表示しようとする機能性の関連性に関する評価が記載されている[注２]。

□表示しようとする機能性の科学的根拠として、査読付き論文として公表されていない。

別紙様式（Ｖ）－１

研究レビューの方法や結果等について、
□別紙様式（Ｖ）－４を添付している。
□データベース検索結果が記載されている[注３]。
□文献検索フローチャートが記載されている[注３]。
□文献検索リストが記載されている[注３]。
□任意の取組として、未報告研究リストが記載されている[注３]。
□参考文献リストが記載されている[注３]。
□各論文の質評価が記載されている[注３]。
□エビデンス総体の質評価が記載されている[注３]。
□全体サマリーが記載されている[注３]。

□各論文の質評価が記載されている[注３]。
□エビデンス総体の質評価が記載されている[注３]。
□研究レビューの結果と表示しようとする機能性の関連性に関する評価が記載されている[注３]。

注１　食品表示基準の施行後１年を超えない日までに開始（参加者１例目の登録）された研究については、必須としない。
注２　各種別紙様式又はその他の適切な様式を用いて記載（添付の研究レビュー論文において、これらの様式と同等程度に詳しく整理されている場合は、記載を省略することができる。）
注３　各種別紙様式又はその他の適切な様式を用いて記載（別紙様式（Ｖ）－４において、これらの様式と同等程度に詳しく整理されている場合は、記載を省略することができる。）

別紙様式（Ｖ）－２

特定保健用食品とは異なる臨床試験方法とした合理的理由に関する説明資料

１．製品概要

商品名	快眠サポート
機能性関与成分名	L-セリン
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２．特定保健用食品とは異なる臨床試験方法（科学的合理性が担保されたものに限る。）とした合理的理由

無作為化二重盲検プラセボ対照クロスオーバー比較試験を実施した。当該製品の摂取の目的が慢性的な睡眠障害に対する効果でなく、日常生活でのストレスによる一時的な睡眠に不満を持った人を対象にしており、一時的な自覚症状の改善を確認する試験であるため、試験期間（摂取期間）を 4 日間とした。また、食品成分を用いて睡眠の機能性評価を行った既報試験[1~3]においても、3～6日間の期間での効果が確認できているため同様の試験系を参考に実施した。

1　新薬と臨床,**52**, 833.2003
2　日本生理人類学会誌,**9**,143.2004
3　*Sleep Biol.Rhythms*,**4**,75-77.2006

別紙様式（Ｖ）－３

表示しようとする機能性の科学的根拠に関する補足説明資料

１．製品概要

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２．補足説明

①科学的根拠資料に記載される試験食品は、試験用に製造された試作品を用いており、当該製品は、味付けのための香料・クエン酸、賦形剤を付加してあります。以下の理由により、科学的根拠に用いた試験食品と当該製品の同一性は失われていないと考えられます。

・機能性関与成分Ｌ－セリンの原材料の配合量が同じであり、当該製品の分析によりＬーセリンの含有量を確認できている。

・製造時および品質安定性の試験においても、添加した香料、クエン酸、賦形剤の影響により機能性関与成分の品質への影響はないことが確認できている。

・同じ形状であり、水への溶解性の違いがないことが確認できている。

②臨床試験では、日常生活で睡眠に不満を感じている方 53 名（このうち参加をとりやめた者８名を除く）を対象に行いました。このうち日常生活でストレスを感じている 27 名での層別解析においても、「寝つき」が有意に改善（P=0.017）しました。このことから、日常生活でストレスを感じている方も主な対象者になると考えられます。また、全被験者の解析において『寝つき』『睡眠維持（熟眠感)』のスコア改善から「しっかりと休みたい方に」、『睡眠維持（熟眠感)』のスコア改善から「途中で目覚める」方も当該製品の主な対象になると考えられます。

試験には、起床直後の主観的睡眠感を評価する自己記入式の質問表（睡眠調査票）を用いました。31 項目の質問からなり、被験者にそれぞれの項目を 6 段階評価で回答いただきます。回答をそれぞれ重みづけされた尺度値を用いてスコア化し、1～29 項目のスコアを因子分析による 5 つの睡眠感に振り分けます。振り分けられたスコアの平均点をそれぞれの因子のスコアとして算出し解析に用いました。質問項目は、『寝つき：昨夜の寝つきは、普段に比べて（良かった，悪かった)。寝ついてから、ウトウトしている状態は普段に比べて（少なかった,多かった)』『睡眠維持（熟眠感)：夜中に目覚めた回数は普段に比べて（多かった，少なかった)。今朝は、普段に比べて、昨夜の睡眠状態が（気になる,気にならない)。寝返りの量。眠りの深さ。』などになります。

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Effects of L-serine ingestion on human sleep

Yukihiko Ito[1*], Satomi Takahashi[1], Manzhen Shen[1], Kohji Yamaguchi[1] and Makoto Satoh[2]

Abstract

To investigate the effects of L-serine intake on human sleep, we conducted two randomized double-blinded crossover studies. In Study 1, healthy subjects who were dissatisfied with their sleep were given L-serine or a placebo 30 min before going to bed. After waking the next morning, subjective sleep quality was rated using the Ogri-Shirakawa-Azumi subjective sleep rating scale. In Study 2, subjective sleep quality was rated using the St. Mary's Hospital sleep questionnaire, and objective parameters, including sleep initiation time, number of nighttime awakenings, and hours of sleep, were evaluated using actigraphy. In Study 1, factors related to "sleep initiation" and "sleep maintenance" during the L-serine intake period were significantly improved compared to the placebo intake period ($p = 0.02$ and $p = 0.008$, respectively). In Study 2, scores for "How well did you sleep last night?" and "How satisfied were you with last night's sleep?" were significantly better during L-serine intake compared to placebo ($p = 0.04$ and $p = 0.03$, respectively). Subjective evaluation of sleep quality on waking was thus improved. In addition, objective evaluation using actigraphy showed that the "number of nighttime awakenings" tended to be decreased ($p = 0.08$). These findings suggest that intake of L-serine before going to bed may improve human sleep.

Keywords: Human sleep; L-serine; Amino acid

Background

Sleep is a basic life process that greatly affects human health. The effects of sleep disturbance or deprivation on the brain, mind and body include not only hypobulia and depression, but also effects potentially leading to hypertension and obesity (Gangwisch et al. 2005), thus impairing human quality of life. According to a World Health Organization study, 1 of every 2 persons with insomnia develops some illness other than sleep disturbance within 1 year and requires medical care (Ustün et al. 1995). The number of individuals suffering from sleep difficulties because of changes in living environment continues to increase. In a survey on the incidence of insomnia, about 20% reported experiencing some difficulty sleeping, and this figure was 30% in elderly persons (Ministry of Health, Labour and Welfare Japan 2008; Zhdanova et al. 2001). Management of insomnia has thus become a social issue.

L-serine is a precursor of other amino acids such as glycine and L-cysteine, and of cell membrane lipids such as phospholipids and sphingolipids. L-serine plays an extensive role in protein synthesis and intracellular metabolism. In knockout mice in whom 3-phosphoglycerate dehydrogenase (PHGDH) in the L-serine synthetic pathway is inactivated, abnormal brain morphogenesis, including microcephaly and absence of specific regions, and brain dysfunction occurs (Yoshida et al. 1980). PHGDH deficiency in humans causes neuropathy and postnatal microcephaly (Pepplinkhuizen et al. 1980; de Koning et al. 2004). This postnatal microcephaly can be improved by L-serine administration during pregnancy (de Koning et al. 2004). Such reports show that L-serine plays an important role in central nervous system (CNS) morphogenesis and function.

Social isolation stress in neonatal chicks on removal from their flock is associated with increased active wakefulness and vocalization (Panksepp et al. 1981; Sahley et al. 1980; Feltenstein et al. 2003). L-serine administration in this model reduces locomotor activity and vocalization, and increases sleeping posture time (sitting motionless with head drooped) (Koutoku et al. 2005; Asechi et al. 2006; Asechi et al. 2008; Shigemi et al. 2010). However, the effects of L-serine on human sleep have not been reported. We therefore conducted two studies to clarify the effects on human sleep of L-serine intake before going to bed.

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Subject and methods

Studies 1 and 2 were both randomized double-blinded crossover studies that included subjects who were dissatisfied with their sleep, mainly sleep latency and nocturnal awakening. Protocols for both studies were reviewed and approved by the institutional review board at FANCL Corp. before being conducted. All subjects were fully informed about the nature and methods of the studies, and informed consent was obtained in compliance with the Declaration of Helsinki.

Study 1 included 53 subjects. During the study period, subjects were not permitted to drink alcohol, stay out overnight, or use any medications or supplements that would affect sleep. They were instructed to maintain their usual eating and lifestyle habits. Each night for 4 consecutive days, 30 min before going to bed, the subjects ingested 3 g of L-serine powder (content: ≥98.5%) or a placebo powder (trehalose). The wash-out period was ≥3 days.

Subjective sleep quality was evaluated in each subject within 30 min after waking the next morning using the Ogri-Shirakawa-Azumi subjective sleep rating scale (OSA), which is used for qualitative evaluation of sleep (Oguri et al. 1985). Scores were calculated for 5 factors as described in a previous report from the results of the subject responses to each item, rated in 6 grades. Mean values for each 4-day period were used for analysis. Factor 1, "morning sleepiness", related to feeling sleepiness on waking in the morning. Factor 2, "sleep maintenance", related to whether the subject experienced waking during sleep. Factor 3, "morning vague anxiety", related to vague anxiety on waking in the morning. Factor 4, "Satisfaction of sleep", related to an intuitive feeling of sound sleep after waking. Finally, factor 5, "sleep initiation", related to sleep onset. For all factors, better sleep quality was indicated by a higher score and poorer sleep quality by a lower score.

Study 2 included 9 subjects who consented to participate. The instructions given during the study period were the same as in Study 1. At night on 2 consecutive days, 30 min before going to bed, the subjects ingested 3 g of L-serine powder or a placebo powder. Subjective sleep quality was evaluated the next morning after waking using the St. Mary's Hospital sleep questionnaire (SMH) (Ellis et al. 1981). The wash-out period was ≥3 days. In this study, the Japanese version of the SMH was used (Uchiyama et al. 1998). Mean values for the 2-day period were used for analysis. An actigraph (familymaicro; Ambulatory Monitoring, Inc., NY, USA) was attached to the non-dominant arm to record the number of body movements, with the results analyzed using AW-2 sleep analysis software (Ambulatory Monitoring, Inc., NY, USA), and sleep/wakefulness was distinguished using Cole's algorithm (Sadeh et al. 1995).

Statistics

OSA and SMH scores were analyzed using Wilcoxon's signed rank test. Actigraphy data were analyzed using the paired t-test.

The level of significance was set at $P < 0.05$. The statistical analyses were performed using the statistical software program StatView for windows version 5.0 (SAS Institute., North Carolina).

Results

Among the 53 subjects in Study 1 who consented to participate, 8 withdrew during the study period. Reasons for withdrawal included use of anti-allergy medication for hay fever in 1 subject, a protocol deviation (drinking alcohol) in 1 subject, and requests to withdraw (change in work environment) in 6 subjects. Data were therefore analyzed from 45 subjects (10 men, 35 women), with a mean age of 35 ± 8 years (range, 26–59 years). Each of these subjects was dissatisfied in some way with their sleep quality. Based on the multiple responses, 23 had difficulty falling asleep, 33 experienced nighttime awakening, and 29 had early morning awakening. The "sleep maintenance" (L-serine, 24.9 vs. placebo, 22.8; $p = 0.02$) and "sleep initiation" (L-serine, 26.9 vs. placebo, 24.7; $p = 0.008$) factor scores were significantly better during L-serine intake compared with placebo (Figure 1). The "morning sleepiness" (L-serine, 24.1 vs. placebo, 22.8; $p = 0.24$), "morning vague anxiety" (L-serine, 26.7 vs. placebo, 24.9; $p = 0.36$), and "Satisfaction of sleep" (L-serine, 23.0 vs. placebo, 22.8; $p = 0.75$) factor scores showed no significant differences.

Among the 9 subjects in Study 2 who consented to participate, 2 withdrew during the study period. Reasons for withdrawal were a protocol deviation (staying out overnight) in 1 subject and "not feeling well" (lip numbness) during the placebo intake period in 1 subject. Data were therefore analyzed from 7 subjects (4 men, 3 women), with a mean age of 35 ± 8 years (range, 25–38 years). Eight of the original 9 subjects complained about difficulty falling asleep and nighttime awakening, and one complained only about nighttime awakening. One subject forgot to attach the actigraph, so actigraphy data were analyzed for 6 patients. Table 1 shows subjective sleep quality results based on the SMH questionnaire. Scores for question "How well did you sleep last night?" ($p = 0.04$) and question "How satisfied were you with last night's sleep?" ($p = 0.03$) were significantly better during L-serine intake compared with placebo. Scores for question "How clear-headed did you feel after getting up this morning?" ($p = 0.06$) were tend to better during L-serine intake compared with placebo.

Subjective evaluation of sleep quality on waking in the morning was improved. No significant differences were seen for any other item. Table 2 shows the results for

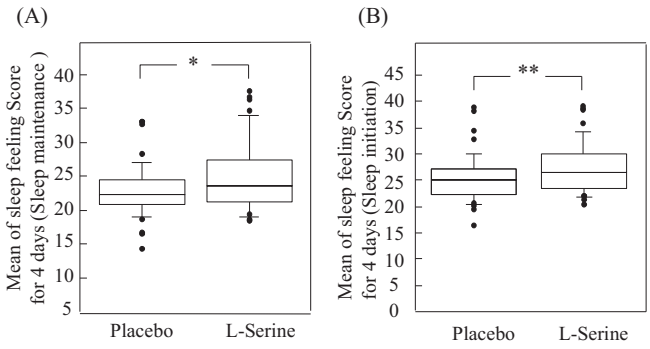

Figure 1 Score of sleep feeling with OSA subjective sleep rating scale. (A) Score of sleep feeling (Sleep maintenance). *Significant difference compared to Placebo by Wilcoxon's signed rank test; $p < 0.02$ ($n = 45$). **(B)** Score of sleep feeling (Sleep initiation). **Significant difference compared to Placebo by Wilcoxon's signed rank test; $p < 0.008$ ($n = 45$).

objective evaluation using actigraphy. The number of nighttime awakenings during L-serine intake tended to be decreased compared with placebo.

Discussion

The results of this study suggest that intake of L-serine before going to bed improves subjective sleep quality among individuals who are dissatisfied with their sleep. The results of objective evaluation using actigraphy also support these findings.

In Study 1, parameters related to nighttime awakening and sleep initiation on the OSA were significantly improved, but Study 2 found no significant improvements in the corresponding items. This may have been influenced by the smaller number of subjects in Study 2 and differences in the questionnaire used. Objective evaluation using actigraphy showed that nighttime awakenings tended to be decreased. In terms of distinguishing sleep/wakefulness, the concordance between actigraphy and polysomnography (PSG) in healthy individuals is ≥90%, and a high concordance of 78-85% has also been reported in patients with sleep disorders (Kushida et al. 2001). However, results from the questionnaires used in our study and actigraphy did not show changes in sleep depth or rapid eye movement (REM) sleep/non-REM sleep. Studies using PSG are needed to identify changes in sleep structure.

With regard to L-serine and reversible conversion to glycine in vivo, oral administration is reported to improve sleep in humans (Inagawa et al. 2006; Yamadera et al. 2007). Glycine is an inhibitory neurotransmitter like gamma-aminobutyric acid (GABA). Shigemi et al. investigated the effects of simultaneous administration of the GABAA receptor antagonist picrotoxin, the glycine receptor antagonist strychnine, and L-serine (Shigemi et al. 2008). They found that the hypnotic effects of L-serine were inhibited by the GABAA receptor antagonist picrotoxin, but not by strychnine. On the other hand, the hypnotic effects of glycine were inhibited by the glycine receptor antagonist strychnine. That report showed that the mechanism of action differs from that for glycine. However, whether a similar mechanism of action exists in humans is unknown from our study.

In a social isolation stress model in neonatal chicks, Furuse et al. compared L-serine-related phosphoserine,

Table 1 Score of St. Mary's hospital sleep questionnaire (Study 2)

Subjective symptom after awake		Placebo	L-serine	P-value
Was your Sleep?	light < deep	3.4 ± 0.8	4.6 ± 1.7	0.09
How many times did you wake up?	time(s)	2.5 ± 2.0	1.9 ± 0.7	0.80
How well did you sleep last night?	badly < well	3.1 ± 0.8	4.2 ± 1.0	0.04
How clear-headed did you feel after getting up this morning?	still very drowsy < alert	2.1 ± 1.0	3.1 ± 1.1	0.06
How satisfied were you with last night's sleep?	unstisfied < satisfied	2.3 ± 0.7	3.3 ± 0.6	0.03
Were you troubled by waking early and being unable to get off to sleep	no < yes	1.2 ± 0.4	1.1 ± 0.2	0.18
How much difficulty did you have in getting off to sleep last night?	none or very little < difficult	1.5 ± 0.3	1.2 ± 0.3	0.15
How long did it take your to fall asleep last night.	mins	18.4 ± 14.9	12.9 ± 9.9	0.73

Values are means ± SD. n =7.
Significant difference compared to Placebo by Wilcoxon's signed rank test.

Table 2 Score of actigraphy items (Study 2)

Actigraphy item		Placebo	L-serine	P-value
Sleep latency	min	12.3 ± 6.0	7.2 ± 1.8	0.46
Sleeping time	min	360 ± 53	366 ± 38	0.56
Arousal time	min	21.6 ± 15.8	18.3 ± 17.6	0.72
Awake frequency	time(s)	8.1 ± 2.2	5.8 ± 3.1	0.08
Long wake episode	time(s)	2.9 ± 1.2	1.4 ± 3.1	0.38

Values are means ± SD. n =6.
Significant difference compared to Placebo by paired t-test.

acetyl serine, lysophosphatidylserine, L-alanine, lysine, methionine, and tryptophan; and reported that L-serine had both hypnotic and anxiolytic effects (Koutoku et al. 2005; Asechi et al. 2008). In addition, D-serine, an optical isomer of L-serine, is present in the vertebrate brain, and particularly in mammals, is an N-methyl-D-aspartate (NMDA) receptor agonist. However, in the neonatal chick model of isolation stress, decreased locomotor activity and vocalization, as well as prolonged sleep-like behavior, were confirmed only with L-serine, while administration of D-serine had no effect (Asechi et al. 2006). Furthermore, measurement of plasma and cerebral cortical levels of L- and D-serine after oral administration in rats showed that L-serine levels increased in both plasma and the cerebral cortex, whereas D-serine did not (Tomonaga et al. 2012). The improvement in human sleep with L-serine observed in our study was thus probably not mediated by D-serine synthesis.

Subjects in our study took L-serine 30 min before going to bed. With oral administration of L-serine to rats, plasma L-serine levels peaked 30 min after administration, then decreased, reaching baseline levels within 10 h (Tomonaga et al. 2012). We have confirmed increased plasma L-serine levels in humans 30 min after L-serine ingestion (data not shown). These results suggest that the timing of L-serine administration in our study was appropriate. In addition, subjects in both Studies 1 and 2 felt refreshed and had no problems the next morning after taking L-serine. No hangover effects of drowsiness were reported the next day.

When taking sleep-improving drugs, resistance after long-term administration or rebound insomnia after discontinuation are frequently problematic. We have shown that when subjects who are dissatisfied with their sleep drink a beverage containing 3 g of L-serine on consecutive days for 1 month, the improvement in sleep quality persists even 1 month after starting administration (data not shown). Moreover, follow-up for 1 month after discontinuing L-serine showed no worsening of sleep quality compared to before administration. Instead, although the effects were diminished compared to during L-serine intake, improved sleep status tended to be maintained. These results indicate no resistance to the effects of L-serine and no problems with rebound insomnia.

In a study of neonatal chicks, L-serine prolonged the time of sleep-like behavior that had been shortened by social isolation stress (Koutoku et al. 2005; Asechi et al. 2006; Asechi et al. 2008; Shigemi et al. 2010). In our Study 1, stratified analysis of 27 subjects who experienced stress in their daily lives also showed a significant improvement in "sleep initiation" ($p = 0.017$). These results demonstrate that L-serine can also improve sleep among individuals suffering from stress.

Our findings suggest that L-serine improves sleep initiation and nighttime awakenings, resulting in improved feelings of having slept well when waking in the morning. L-serine may represent a good option for individuals who suffer from difficulty sleeping.

Conclusion

The results of this study suggest that consecutive intake of L-serine is effective for individuals experiencing sleep difficulty. L-serine may be a good choice for most individuals affected by poor sleep.

Abbreviations

PHGDH: 3-phosphoglycerate dehydrogenase; CNS: Central nervous system; OSA: Ogri-Shirakawa-Azumi subjective sleep rating scale; SMH: St. Mary's Hospital sleep questionnaire; PSG: Polysomnography; REM: Rapid eye movement; GABA: Gamma-aminobutyric acid; NMDA: N-methyl-D-aspartate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YI conceived the study, designed the study, performed study, analyzed the data, performed the statistical analysis and drafted the manuscript. ST conceived the study, and drafted the manuscript. MS helped to design the study, analyzed the data. KY helped to conceive the study and helped to draft the manuscript. MS conceived the study and edited the manuscript critically. All authors read and approved the final manuscript.

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