

## REVIEW PAPER

## A Review of the Potential Efficacy of Alpha-S1-Casein Tryptic Hydrolysate on Stress and Sleep Disorder

*Chee Huei Phing*

Faculty of Science, Universiti Tunku Abdul Rahman,  
31900 Kampar, Perak, Malaysia

### Abstract

**Introduction:** Sleep, much like eating, is a pivotal part of life. The mechanisms of sleep are only partly clear and are the subject of future intense research. Scientific evidence behind sleep-promoting supplements such as alpha-s1-casein tryptic hydrolysate is briefly described. These are reviewed using data from clinical trials. Although there are clear physiological connections behind these effects, the clinical relevance has to be studied further. This review seeks to serve as a reference for future clinical trials to promote sleep. **Methods:** Potentially eligible papers were screened at the title and abstract level; of which full text papers on human-based trial were retrieved. Papers were also identified from screening of reference lists. **Results:** A literature search was undertaken between Year 2005 to Year 2016 using database Google Scholar. Search terms were “Effects of alpha-s1-casein tryptic hydrolysate”. A total of seven studies were reviewed and summarized. **Conclusion:** Randomized controlled trial in human being is warranted to unearth the potential benefits of  $\alpha_{s1}$ -casein tryptic hydrolysate for Malaysian adults.

**Keywords:** Sleep, Alpha-S1-Casein Tryptic Hydrolysate, Stress

### Introduction

Problems in staying asleep, falling asleep, waking up too early every morning, are the primary indication of insomnia. Several studies denoted that approximately 25% to 36% of adults experience occasional or transient insomnia<sup>1,2,3,4,5,6</sup>. Chronic insomnia was observed in 7.5% to 15% of adult. It is well evidenced that insomnia can bring to numerous adverse outcomes at individual and community levels. Chronic sleep debt brings to daytime tiredness and fatigue,

impairments in cognitive functions such as memory loss and lacks of concentration<sup>7,8</sup>. Anxiety, stress and depression are usually observed among insomniac people<sup>9,10,11</sup>. In addition, studies have concluded that sleep insufficiency can lead to the development of chronic diseases such as obesity, diabetes mellitus and high blood pressure<sup>12,13</sup>. Insomnia leads to poor work performance, absenteeism, decreased productivity and enhanced work-related accidents<sup>8</sup>, raised healthcare costs and decreased quality of life<sup>14,15</sup>.

Insomnia is believed to be chronic if it happens on three nights weekly for one month or more. Chronic insomnia is related to anxiety, stress and mild depression<sup>16,17</sup>. Anxiety and stress influence the sleep/wake rhythm and alterations both in sleep architecture and in sleep duration<sup>18</sup>.

Knowing that chronic insomnia are related to anxiety, stress and mild depression<sup>9,19,10</sup>, it may be postulated that therapies which decrease stress could be beneficial to individuals suffering from sleep disorders<sup>9</sup>. Stress is a psychological answer to a pressure of the individual's environment, which can be sized up psychologically.

Prolonged stress can be noxious in several areas such as sleep<sup>20</sup>, memory<sup>21</sup> and feeding behaviour<sup>22</sup>. Stress may elevate the risk of chronic disorders and alter healthy lifestyle behaviours.

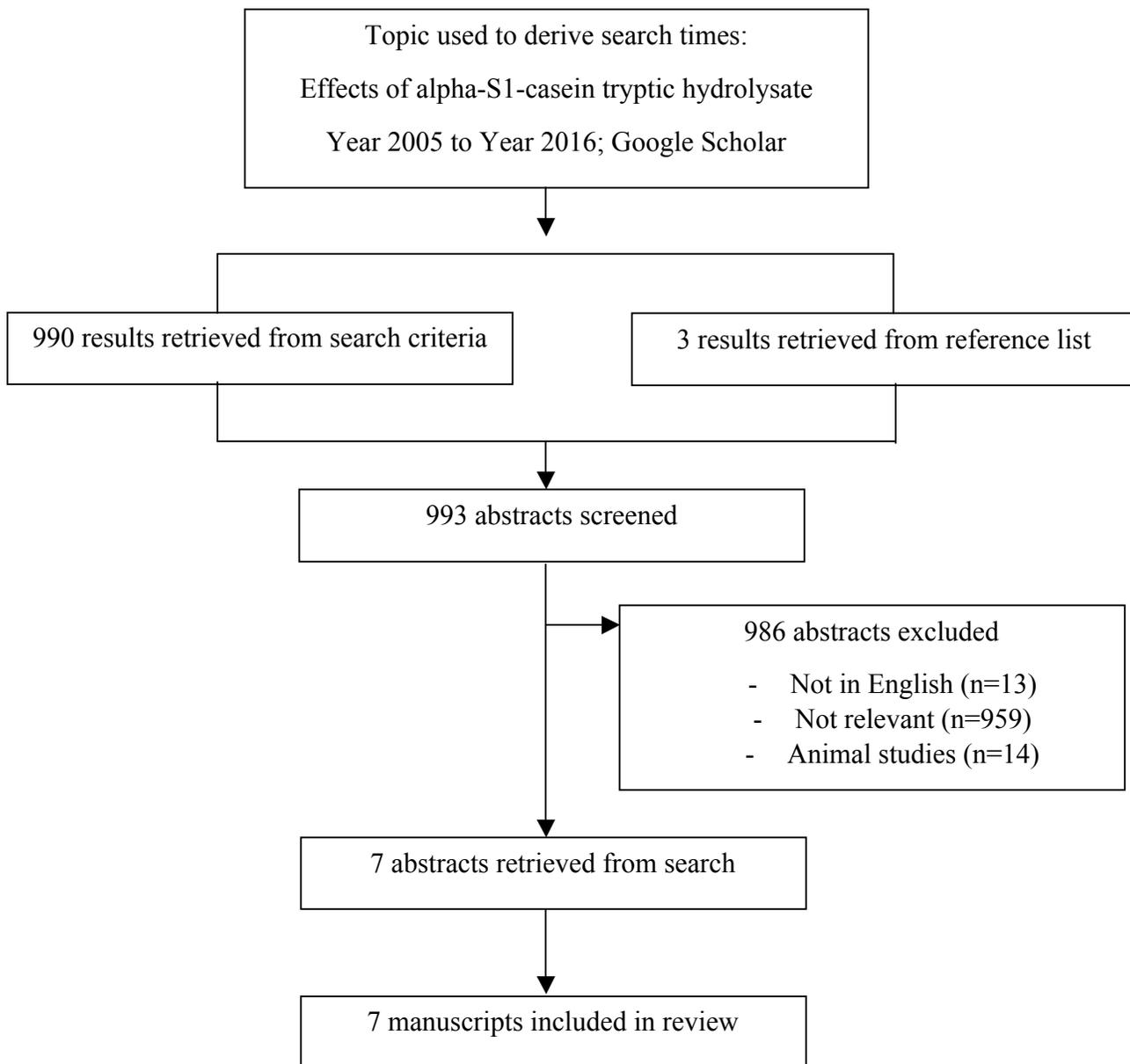
Our society may have thus far underestimated the roles that sleep plays in wellness and health. Research is mounting that correlates "short sleep" with dysfunction in numerous pivotal domains of wellness: cognitive, metabolic and psychological. "Short sleep" is regarded as habitual sleep duration of less than six hours every night<sup>23</sup>. It is well evidenced that lifestyle factors such as poor diet, sedentary

lifestyles and smoking are leading causes of mortality. In addition, chronic sleep deprivation has been demonstrated to be associated with an increased risk of all-cause mortality and risk of cardiovascular disease, obesity, high blood pressure, diabetes mellitus and cancer<sup>24,25,26</sup>.

Living organisms have circadian rhythms or intrinsic biological clocks that establish the timing of basic physiological occurrences, such as the sleep/wake rhythm. These rhythms cycle roughly every 24 hours, and it is pivotal for the living organisms to coordinate its internal cycle to the external environment (daylight and night time) for survival and wellbeing<sup>27</sup>. The brain fundamentally requires changes in autonomic and electrical activity approximately every 24 hours to maintain homeostasis in many domains. These changes are necessary to enable memory and learning to function ideally as well as manage brain energy balance in order to rejuvenate and restore brain cells.

## Methods

Potentially eligible papers were screened at the title and abstract level; of which full text papers on human-based trial were retrieved. Papers were also identified from screening of reference lists.



**Figure 1.**

## Results

**Table 1.** Summary of human studies on alpha-s1-casein tryptic hydrolysate

Study population	Study design	Sample size	Dosage	Description of findings
Day-time workers from the general population of Japan <sup>28</sup>	Double-blind, controlled, parallel study of five weeks in total, including a follow-up period of one week  Data collection at 1 <sup>st</sup> , 15 <sup>th</sup> and 30 <sup>th</sup> day of treatment period	32 subjects, aged between 25 and 40 years	Two weeks treatment with alpha-S1-casein tryptic hydrolysate	- Sleep quality (Pittsburg Sleep Quality Index) After two weeks: Improves sleep quality After four weeks: Decreases sleep latency, decreases daytime dysfunction
63 female volunteers showing at least one stress symptom in France <sup>29</sup>	Double-blind, cross over study	63 female volunteers	Received alpha-S1-casein tryptic hydrolysate for 30 days	A significantly greater positive evolution of stress symptoms in five different areas was demonstrated in the group taking alpha-S1-casein tryptic hydrolysate compared to the one taking the placebo: The digestive, cardiovascular, intellectual, emotional and social problem areas  The effect of alpha-S1-casein tryptic hydrolysate was greater in subjects having a high intensity score for a major symptom at the beginning of the study
Healthy human volunteers facing successive mental and physical	Randomized, double-blinded, placebo controlled study	42 healthy male subjects	Two-200 mg capsules of alpha-S1-casein tryptic hydrolysate / placebo (bovine	Stroop test and stroop test plus cold pressure test increased systolic blood pressure, diastolic blood pressure and heart rate. Lower percentage changes in

<p>stress situations in Paris, France<sup>30</sup></p>			<p>skimmed milk powder)</p>	<p>systolic blood pressure and diastolic blood pressure of the treatment group</p> <p>A significant decrease of the plasma cortisol concentration in the treatment group but not in the placebo group through the stroop test plus cold pressure test</p> <p>Heart rate remained stable in treatment group between the initial rest period and the cold pressure test unlike what happened in placebo group</p>
<p>Healthy women<sup>31</sup></p>	<p>Random-assignment double-blind trial</p>	<p>27 healthy women (13 in treated group; 14 in control group)</p>	<p>150 mg oral intake of <math>\alpha</math>-casein tryptic hydrolysate for 30 days</p>	<p>No difference was observed between treatment group and control group in low stress responders and high stress responders at Day-0. At Day-11 and Day-31, the systolic blood pressure stress response was significantly lower in treatment group and control group high stress responders, while there was no nutrient effect in low stress responders</p> <p>The chronic intake of 150 mg daily bovine milk alpha-s1-casein tryptic hydrolysate reduces the systolic blood pressure response to the stroop test in high stress responder women</p>
<p>Healthy human male volunteers<sup>32</sup></p>	<p>Double blind placebo controlled study</p>	<p>40 healthy human male volunteers</p>	<p>Two 200 mg capsules of hydrolysate (treatment group) or</p>	<p>Treatment group subjects showed significantly lower increases in systolic blood pressure, in diastolic blood</p>

			<p>placebo (skimmed milk) in the morning and in the evening the day before, and two other capsules in the morning, two hours before being tested</p>	<p>pressure and a significant decrease in plasma cortisol levels in comparison with control group subjects</p> <p>No significant difference was found between treated and control subjects with respect to heart rate change</p>
<p>Female volunteers in Korea<sup>33</sup></p>	<p>Double-blind, randomized, crossover, placebo-controlled trial</p>	<p>63 female volunteers suffering from at least one disorder that may be related to stress such as anxiety, sleep problems and general fatigue</p>	<p>Receive either tablets containing alpha-s1-casein tryptic hydrolysate or placebo at the dose of 150 mg/day for 30 days</p> <p>After a 3 weeks washout period, they were crossed over for a new 30-day period of tablets intake</p>	<p>The 30-day treatment by alpha-s1-casein hydrolysate in females with stress-related symptoms reduced their symptoms, particularly in digestion, cardiovascular, intellectual, emotional and social problems</p>
<p>Ten national and international calibre biathletes from a Military Base in Quebec<sup>34</sup></p>	<p>Intervention trial</p>	<p>10 national and international calibre biathletes from a Military Base in Quebec</p>	<p>The subjects were subjected to four weeks of rigorous training and various blood tests were conducted to measure cortisol levels. Training intensity was increased by 10% each week</p>	<p>The mean cortisol level in athletes taking alpha-s1-casein tryptic hydrolysate was significantly lower at week-4 compared to the basal level observed during the first week, while it was higher in athletes taking placebo</p>

## Discussion

Milk proteins are among the most extensively consumed human food proteins. Milk protein comprises insoluble colloidal casein and soluble whey protein. Caseins account for 76% to 86% of the total milk proteins and can be characterized by major gene products explicitly alpha-s1-casein, alpha-s2-casein, beta-casein and kappa-casein<sup>35</sup>. A milk alpha-s1-casein hydrolysate and a bioactive decapeptide (alpha-s1-casein-(f91-100), alpha-casozepine) have demonstrated an anxiolytic-like profile in the conditioned defensive burying test<sup>36</sup>.

The benzodiazepines were presented for the treatment of anxiety and insomnia in the 1960s. These medications were demonstrated to have unfavourable effects such as ataxia, amnesia, hypotension, nausea, tiredness, leucopenia, confusion, depression and hostility<sup>37</sup>, dependence and tolerance<sup>38,39</sup>. Benzodiazepines are still in use for the treatment of insomnia. However, they are less frequently prescribed at present, due to those concerns regarding dependence and abuse, movement and memory impairment and residual effects<sup>40</sup>.

A newer class of medications, recognized as “non-benzodiazepine, benzodiazepine receptor agonists” were introduced for the treatment of insomnia in the 1990s<sup>41,42</sup>. These drugs are highly effective in promoting sleep and appearing to have better safety profiles but are associated with residual effects.

An alternative approach is to emphasize natural substances. Cow’s milk has long been reflected by folk wisdom as a calming beverage promoting sleep. It was revealed that adults taking a meal of milk and cornflakes tend to have uninterrupted sleep<sup>43</sup>, and it was demonstrated that evening

consumption of lactalbumin may enhance sleep and morning alertness<sup>44</sup>.

It was revealed that bovine alpha-s1-casein tryptic hydrolysate containing a decapeptide, demonstrated anxiolytic-like effects in animal studies<sup>45,46</sup> and enhances sleep in rats exposed to chronic mild stress<sup>47</sup>. This tryptic hydrolysate demonstrated anxiolytic-like effects, without side effects, on the hemodynamic parameters under physically and mentally stressful conditions among healthy human volunteers<sup>30</sup>.

Milk proteins are the only proteins produced by mammals to feed their young. Caseins are nitrogen providers for the new-borns, which produce peptides with several biological activities through enzymatic hydrolysis<sup>48</sup>. The peptides are opioid and opioid-antagonist peptides, angiotensin-converting enzyme inhibitors, platelet-aggregation inhibitors, immunostimulating peptides, phosphopeptides carriers of minerals ( $\text{Ca}^{2+}$ ,  $\text{Fe}^{2+}$ ), antibacterial peptides, mitogenic peptides and protease inhibitors.

The quality and quantity of sleep have a great impact on daily life. Sleep deprivation influences ability to interact with others, concentration and work. The need for sleep differs individually and longer sleep duration does not essentially lead to alertness in the morning.

To observe a long-lasting and bright future for supplements that truly promote sleep, the following must be considered:

- Alpha-s1-casein tryptic hydrolysate are not magic pills. Factors contributing to stress and sleep disorder should be scrutinized in the broader context.
- Clinical proofs are warranted. Before taking into consideration new formulation,

probable efficacy of alpha-s1-casein tryptic hydrolysate must be confirmed by clinical trials.

### Conclusion

Sleep disorder is an emerging and long standing health concern. There is an essential need for tailored food ingredients demonstrating true clinical potential for promoting sleep. Randomized controlled trial in human being is warranted to unearth the potential benefits of  $\alpha_{s1}$ -casein tryptic hydrolysate for Malaysian adults.

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**Corresponding Author**

Chee Huei Phing, PhD  
Faculty of Science,  
Universiti Tunku Abdul Rahman,  
31900 Kampar, Perak, Malaysia  
**Tel:** 05-468 8888 Extension 4526

**Email:** cheehp@utar.edu.my