

# Double-Blind Placebo and Active (Caffeine) Controlled Study to Examine the Effects of the Herbal Nutritional Supplement Beverage “Wake Up®” on Vigilance and Function after Lunch

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**ABSTRACT:** **Background:** Post-lunch dip is a well-known phenomenon that results in a substantial deterioration in function and productivity after lunch.

**Objectives:** To assess whether a new herbal-based potentially wake-promoting beverage is effective in counteracting somnolence and reduced post-lunch performance.

**Methods:** Thirty healthy volunteers were studied on three different days at the sleep clinic. On each visit they ate a standard lunch at noontime, followed by a drink of “Wake up®,” 50 mg caffeine, or a placebo in a cross-over double-blind regimen. At 30 and 120 minutes post-drinking, they underwent a battery of tests to determine the effects of the beverage. These included: a) a subjective assessment of alertness and performance based on a visual analog scale, and b) objective function tests: the immediate word recall test, the digit symbol substitution test (DSST), and hemodynamic measurements. The results of the three visits were compared using one-way analysis of variance, with  $P < 0.05$  considered statistically significant.

**Results:** In all performance tests, subjective vigilance and effectiveness assessment, both Wake up® and caffeine were significantly superior to placebo 30 minutes after lunch. However, at 2 hours after lunch, performance had deteriorated in those who drank the caffeine-containing drink, while Wake up® was superior to both caffeine and placebo. Blood pressure and pulse were higher 2 hours after caffeine ingestion, compared to both Wake up® and placebo.

**Conclusions:** These results suggest that a single dose of Wake up® is effective in counteracting the somnolence and reduced performance during the post-lunch hours. In the current study it had no adverse hemodynamic consequences.

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**KEY WORDS:** herbs, post-lunch dip, vigilance, Wake up®

Post-lunch dip results in a substantial deterioration of function and productivity. There are several potential explanations. One possibility is that this is a circadian phenomenon, occurring regardless of food intake [1]. It may be an evolutionary phenomenon since animals in savannas prefer to take a mid-day nap [2]. A potential mechanism to explain this phenomenon is the sharp drop in cortisone/cortisol levels in the early afternoon that would explain the tendency to sleep [3]. Another explanation lies in body temperature changes. When body temperature decreases, as occurs in the early afternoon hours, the tendency to sleep increases [2]. A heavy meal may alter the distribution of blood flow, resulting in an increase to the intestine and a decrease to the brain, which causes sleepiness [4]. Irrespective of the mechanism, this post-lunch dip for 2–3 hours after lunch has been shown to have a substantial impact on work performance. During these hours there is reduced productivity and decreased quality of work, as well as an increase in errors and work accidents [5].

Many chronic medical conditions may result in fatigue, sleepiness, and difficulty concentrating during work hours. Some examples are obstructive sleep apnea syndrome [6], fibromyalgia [7], heart failure, depression and others. It was recently shown that in Israel only 48% of obstructive sleep apnea patients recommended for CPAP (continuous positive airway pressure) actually purchase the device [6]. When there is a preexisting condition that results in somnolence, the post-lunch dip may be even more profound, resulting in accidents and injuries.

A wake-promoting nutritional supplement may reduce these phenomena. One potential way to achieve this is by drinking coffee [8]. Caffeine blocks adenosine receptors A1 and A2A. Adenosine inhibits the release of neurotransmitters and is known to play an important role in sleep homeostasis [8]. Adenosine causes sleepiness by inhibiting cholinergic neurons which are responsible for arousal [8]. Indeed, it was

\*Ola Kassis performed this study as a part of her MD thesis project

found that drinking coffee, as compared to decaffeinated coffee, at lunch improves alertness and performance [9]. On the other hand, caffeine results in a rebound effect: namely, sleepiness that follows a decrease in caffeine levels in the blood as well as possible dependence [8]. Moreover, caffeine has a short half-life and potential side effects such as increases in pulse rate and blood pressure [8]. In addition, regular coffee drinking results in tolerance and the subsequent substantial reduction in the caffeine effect [8]. The newly developed “Wake up<sup>®</sup>” beverage (C.O.L. Group Ltd, Tel Aviv, Israel) is a wake-promoting nutritional supplement based on herbal extracts of guarana, *Ginkgo biloba*, elderberry and “Fruit up<sup>®</sup>” (Wild, Spain, a fruit extract containing predominantly fructose). It was previously shown that guarana improves memory performance and mood and increases alertness [10]. Extracts of *Ginkgo biloba* are used in herbal medicine for asthma and cardiovascular disease and have been shown to benefit memory [11]. The main active constituents of ginkgo belong to two distinct chemical groups: the biflavone glycosides and sesquiterpene trilactone bilobalide. Most of the pharmacological and clinical work carried out on ginkgo used an extract containing both classes of compounds, and these extracts are proven antioxidants and vasodilators and can increase cerebral blood flow in animals. Extracts also possess neuroprotective potential, thought to be mediated via inhibition of nitric oxide synthesis [11]. Fruit up<sup>®</sup> mainly adds taste to the Wake up<sup>®</sup>, although its glucose content may also improve alertness [12]. In the current study, we examined whether Wake up<sup>®</sup>, as compared to caffeine and placebo, improves vigilance and function following lunch, and tested the duration of the effect at 30 and 120 minutes after drinking. We hypothesized that drinking Wake up<sup>®</sup> after lunch improves short-term memory and function similarly to caffeine, but better than placebo, and that the effect is longer with Wake up<sup>®</sup> compared to caffeine. We expected that it would affect blood pressure and pulse rate to a lesser extent compared to caffeine.

## SUBJECTS AND METHODS

Thirty healthy non-smoking volunteers were recruited via advertisements at the Technion Faculty of Medicine. Most were students or faculty staff. They were all over 18 years old and of both genders. All were in stable medical condition, free of chronic diseases and not taking medications. The study was approved by the Rambam Institutional Review Board and all participants signed an informed consent prior to participation. At the first study visit they were given an explanation about the study, signed the consent form, and were trained with the performance tests. Thereafter, the study consisted of three additional visits, with  $6 \pm 3$  days between each visit. All three study visits were performed in a similar fashion, at an identical time of day, as described below.

## STUDY PROCEDURE

At each visit, participants reported to the study room around noontime. They were given a similar and standardized lunch between 12:00 and 13:00, after which they drank one small bottle containing Wake up<sup>®</sup>, 50 mg caffeine, or a placebo in a cross-over double-blind regimen. All three drinks had a similar look and taste (which were specifically prepared for this study by a flavor and fragrance-producing company), and were in a similar 100 ml bottle. Volunteers were asked to maintain a stable and regular schedule and a stable sleep/wake regimen during the study period.

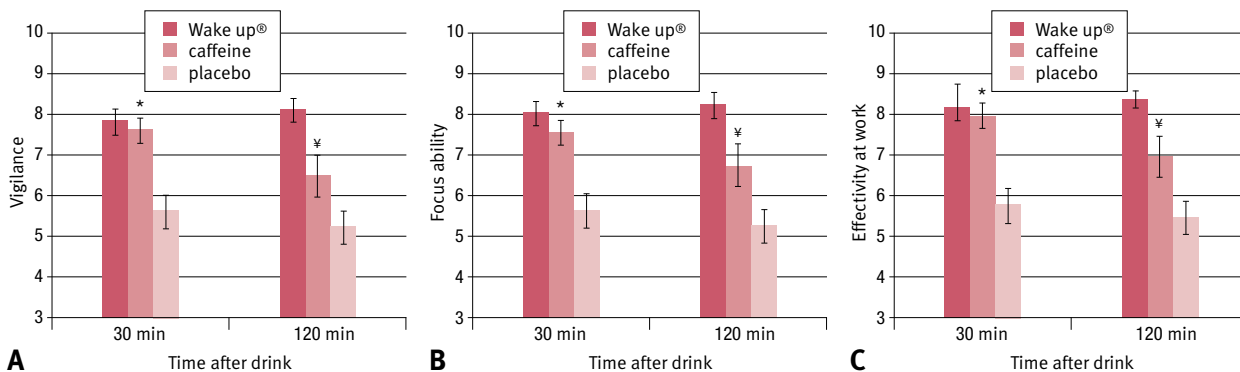
They were also asked to consume a similar breakfast on the three mornings of the study visits. Each visit had the same routine: participants ate lunch and immediately drank 100 ml of beverage (Wake up<sup>®</sup>, caffeine, or placebo). At 30 minutes and 120 minutes after drinking, they underwent a battery of tests including measurement of vital signs, blood pressure, immediate word recall test (short-term memory), digit symbol substitution test (concentration), and subjective rating (on a visual analogue scale) of their vigilance, ability to focus, and effectiveness at work. The results of the three visits were compared utilizing one-way analysis of variance, with  $P < 0.05$  considered statistically significant.

## PSYCHOMOTOR/COGNITIVE AND BEHAVIORAL TESTS

- VAS – a 10 cm scale according to which the participant ascribes his/her subjective feeling regarding the parameters. The three parameters in the scale were: somnolent – alert; confused – focused; and non-effective – effective in performance/work. Subjects were asked to mark the scale line according to their state at each test, and the score was calculated as the length (in cm) from the left side of the line to the point that they marked. Thus, the numbers run from 0 to 10, with higher scores indicating greater subjective alertness or better performance. These scales are widely used to assess subjective complaints, including somnolence [13].
- DSST (Digit Symbol Substitution Test) [14] – a time-limited exercise during which the subject is required to replace digits by symbols within a given time restriction (2 minutes). This test provides data on the accuracy and rate of performing the task and is commonly used to assess function and to compare between various sleep/alert conditions [15].
- iWRT (immediate Word Recall Test) – a short-term memory test commonly used to assess cognitive function and to compare between various sleep/alert conditions [16]. Thirty unrelated words were presented to the participant, each word for 2 seconds, after which the participant was required to recall as many words as s/he could. Both correct and incor-

VAS = visual analogue scale

**Figure 1. [A]** The effect of drink content and time after the drink on participants' rating of their vigilance (on a VAS). \**P* < 0.05 Wake up<sup>®</sup> and caffeine vs. placebo, †*P* < 0.05 Wake up<sup>®</sup> vs. caffeine and placebo  
**[B]** The effect of drink content and time after drink on participants' rating of their ability to focus (on a VAS). \**P* < 0.05 Wake up<sup>®</sup> and caffeine vs. placebo, †*P* < 0.05 Wake up<sup>®</sup> vs. caffeine and placebo  
**[C]** The effect of drink content and time after drink on participants' rating of their effectiveness at work (on a VAS). \**P* < 0.05 Wake up<sup>®</sup> and caffeine vs. placebo, †*P* < 0.05 Wake up<sup>®</sup> vs. caffeine and placebo



rect or repeated words were analyzed. The iWRT has been shown to reliably quantify short-term memory as a function of the frontal lobe [17], which can be impaired by sleepiness and improved by alertness [18].

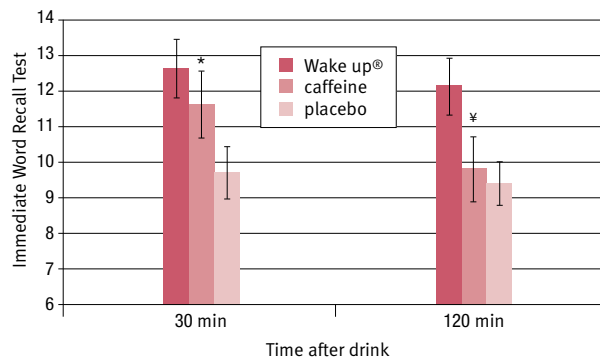
**RESULTS**

All 30 volunteers (13 males, 17 females) completed the study. Their age and body mass index were 36.6 ± 12.4 years (range 18–61 years) and 24.3 ± 3.5 kg/m<sup>2</sup> (range 17.0–31.8 kg/m<sup>2</sup>), respectively. In all performance tests and subjective vigilance and effectiveness assessments, both Wake up<sup>®</sup> and caffeine were significantly superior to placebo 30 minutes after lunch. However, 2 hours post-lunch, performance after ingestion of the caffeine-containing drink deteriorated, with Wake up<sup>®</sup> being superior to both caffeine and placebo. The VAS rating of vigilance, ability to focus, and performance (effectiveness) at work are presented in Figure 1 A-C, respectively. As can be seen in all three parameters 30 minutes after the drink, both caffeine and Wake up<sup>®</sup> resulted in significant improvement.

However, 2 hours after the drink there was a decrease in the self-rating after caffeine (in all three parameters), and only after Wake up<sup>®</sup> did vigilance and performance remain high. Thirty minutes after the drink the number of correct words recalled was 12.6 ± 4.1 with Wake up<sup>®</sup>, compared to 11.6 ± 4.8 and 9.7 ± 3.8 with caffeine and placebo, respectively (*P* < 0.05 for both caffeine and Wake up<sup>®</sup> compared to placebo). However, 2 hours after the drink the number of words recalled was 12.1 ± 4.3 with Wake up<sup>®</sup>, compared to 9.8 ± 4.9 and 9.4 ± 3.5 with caffeine and placebo, respectively (*P* < 0.05 for Wake up<sup>®</sup> compared to both caffeine and placebo) [Figure 2]. The number of correct symbols in the DSST 30 minutes and 120 minutes after the different drinks is demonstrated in Figure 3. As can be seen, at both time points the best performance

DSST = Digit Symbol Substitution Test

**Figure 2.** Number of correct words recalled in the immediate word recall test 30 minutes and 120 minutes after the various drinks. \**P* < 0.05 Wake up<sup>®</sup> and caffeine vs. placebo, †*P* < 0.05 Wake up<sup>®</sup> vs. caffeine and placebo



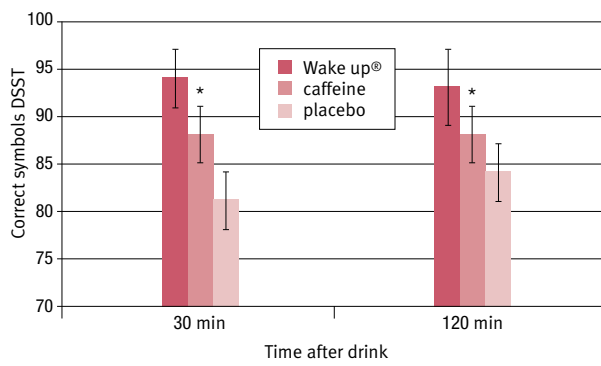
**Table 1.** Hemodynamic measures with the various beverages at 30 and 120 minutes after the drink

|          | 30 minutes after the drink |             |              | 120 minutes after the drink |             |              |
|----------|----------------------------|-------------|--------------|-----------------------------|-------------|--------------|
|          | Pulse                      | Systolic BP | Diastolic BP | Pulse                       | Systolic BP | Diastolic BP |
| Wake up  | 72 ± 10                    | 113 ± 13    | 71 ± 9       | 73 ± 8                      | 112 ± 13    | 71 ± 7       |
| Caffeine | 77 ± 10*                   | 119 ± 13*   | 75 ± 9**     | 73 ± 8                      | 117 ± 14    | 74 ± 9       |
| Placebo  | 74 ± 13                    | 115 ± 13    | 71 ± 7       | 73 ± 10                     | 112 ± 15    | 70 ± 7       |

\**P* < 0.05 caffeine vs. Wake up<sup>®</sup>

\*\**P* < 0.05 caffeine vs. both Wake up<sup>®</sup> and placebo

**Figure 3.** Number of correct symbols in the DSST (Digit Symbol Substitution Test) 30 minutes and 120 minutes after the various drinks. \* $P < 0.05$  Wake up<sup>®</sup> vs. placebo



was observed after the subjects drank Wake up<sup>®</sup> ( $P < 0.05$  between Wake up<sup>®</sup> and placebo). Pulse rate and blood pressure were significantly higher at 30 minutes after the caffeine drink than after the Wake up<sup>®</sup> beverage:  $77.4 \pm 1.9/\text{min}$  vs.  $71.9 \pm 1.8/\text{min}$ , and  $119/75$  vs.  $113/71$  mmHg,  $P < 0.05$  for both. Two hours after the drink, pulse rate and blood pressure were similar for the three beverages [Table 1].

## DISCUSSION

This study shows that Wake up<sup>®</sup> had a subjective rating of alertness, focusing ability, and objective functions (short-term memory and performance) during the first 30 minutes after lunch, similar to the effect of 50 mg caffeine, but a higher subjective rating than caffeine 2 hours later. In addition, unlike caffeine, Wake up<sup>®</sup> did not result in adverse hemodynamic effects.

Post-lunch dip has an important impact on work performance during the 2 hour period after lunch [5]. Most reviews on sleep, sleepiness and safety in shift work indicate that accident risk is increased during this period and that the reason is sleepiness/fatigue [19]. Thus, a wake-promoting drink such as caffeine [8] may reduce this phenomenon; however, several factors should be considered. First, there may be habituation and tolerance to caffeine [20]. Second, caffeine may induce various acute cardiovascular effects, including high blood pressure [20]. Caffeine effectively antagonizes the adenosine receptors. As adenosine receptor stimulation induces vasodilation in most vascular beds, caffeine might well induce vasoconstriction and increase blood pressure. In addition, acute administration of coffee or caffeine increases the cAMP cascade and circulating concentration of epinephrine, and to a lesser extent norepinephrine [20]. Thus, imbibing coffee to alleviate the post-lunch dip is effective but these disadvantages should be considered. The question as to whether coffee intake increases the risk of coronary heart disease remains controversial [20].

In a recent large prospective study, coffee consumption was reported to be inversely associated with total and cause-specific mortality after adjustment for tobacco-smoking status and other potential confounders. Whether this was a causal or associational finding cannot be determined from the data [21]. Inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer [21]. Friedman et al. [21] showed that people who consumed six cups of coffee or more have the lowest hazard ratio for death. However, at this level of coffee consumption, tolerance to the effects of caffeine frequently develops [20] and its effect on counteracting the post-lunch dip remains to be tested. Evans and Griffiths [22] provided clear evidence of complete tolerance to the effects of caffeine on the human central nervous system [22]. In addition, near-complete tolerance, in terms of both humoral and hemodynamic variables, was shown to develop over the first 1–4 days of caffeine use [23]. Hence, a vigilance-promoting drink that does not cause adverse hemodynamic changes could be beneficial.

The newly developed “Wake up<sup>®</sup>” beverage is based on herbal ingredients comprising extracts of guarana, *Ginkgo biloba* and elderberry, together with “Fruit up<sup>®</sup>.” It has already been shown that guarana improves mood and memory performance and increases alertness [10]. In addition, extract of *Ginkgo biloba* also promotes vigilance and has a favorable effect on memory [11]. The Fruit up<sup>®</sup> enhances the taste of the beverage, while its glucose content may also improve alertness [14]. When blood glucose levels drop, such as after lunch or in the post-lunch dip, fatigue and reduced function occur [24]. In fact, we have previously shown that the human response to substantial hypoglycemia is deepening sleep and a diminished counter-regulatory hormonal response [25]. The Fruit up (fructose) content in Wake up<sup>®</sup> could also improve the functioning characteristic. Since neither placebo nor caffeine beverages contain fructose, this study cannot differentiate between the effects of the various components of the beverage. Regardless of the specific ingredient, Wake up<sup>®</sup> has the potential to alleviate the undesired effects of the post-lunch dip. Indeed, regarding vigilance and ability to focus and the tests of short-term memory and function, Wake up<sup>®</sup> showed superiority over placebo, and 2 hours after the drink also over 50 mg caffeine. Importantly, in contrast to caffeine, our study demonstrated that Wake up<sup>®</sup> did not result in adverse hemodynamic effects.

Our study has several limitations. First, the study visits took place between noontime and 15:00, but we did not objectively control for sleep on the night prior to the study, the content of breakfast, or physical activity during the day. Although participants were asked to maintain their regular routines, these were not objectively measured. However, there is no reason to believe that there was a directional skew

in this regard, and the participants or study personnel could not know what every participant would drink on each visit. Thus, we believe this potential bias is random and does not affect the results. Second, the number of participants is not large. Although the sample size does have a power > 0.8 and the differences are of statistical significance, larger cohorts would strengthen our findings. Third, our study examined only the effect of an acute single dose of Wake up<sup>®</sup> and did not evaluate potential habituation or tolerance to its long-term use. These effects should be tested in future studies. It is possible that similar to caffeine, with multiple daily doses there will be tolerance to the effects of Wake up<sup>®</sup> as well. Fourth, our study aimed at testing only the effects of the beverage and not its mechanism of action. The mechanism of action of this beverage is currently unknown and needs to be elucidated. Finally, the participants in our study were healthy. We cannot predict how these beverages would affect specific patients such as those with obstructive sleep apnea, fibromyalgia, heart failure, depression or other illnesses resulting in fatigue, and the results at this time cannot be generalized.

**CONCLUSIONS**

Despite the above-mentioned limitations, our findings strongly suggest that drinking Wake up<sup>®</sup> after lunch improves vigilance and performance similarly to caffeine and significantly better than placebo at 30 minutes after the drink. At 120 minutes, performance and vigilance with Wake up<sup>®</sup> remains high and is significantly superior to both placebo and caffeine. Compared with caffeine, Wake up<sup>®</sup> was not associated with increased pulse and blood pressure in the short term. Thus, Wake up<sup>®</sup> appears to be an appropriate and effective drink to counteract the somnolence and reduced performance during the post-lunch hours. Additional research is required to establish these effects in larger scale studies and to examine the result of multiple daily use.

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“How beautiful it is to do nothing, and then rest afterward”

Spanish proverb